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MENINGOCOCCUS MENINGITIS

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WITH 4 PLATES, 31 FIGURES, 2 IN COLOR, AND 4 CHARTS

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PREFACE

In the preparation of this volume the aim of the authors has been to present in compact form our present knowledge of meningococcus infection of the meninges. As its purposes are practical and it is intended for the use of students and physicians engaged in clinical work, only so much of technical detail has been included as can be carried out with ordinary laboratory facilities. We have not deemed it expedient to burden the volume with minute and detailed laboratory directions, which can be of interest only to the special worker in this field. The physician at the bedside can avail himself only of those diagnostic and therapeutic means which are supplied to him by the equipment of the ordinary general hospital.

In the preparation of the volume a large number of authorities have been consulted, a number too large to be individually enumerated here. We must, however, acknowledge the invaluable aid received from the perusal of the admirable monographs of Councilman, Mallory and Wright, Goeppert, Busse, Elser and Huntoon, and especially the recently published volume of Netter and Debré.

We have appended bibliographic references at the

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end of nearly every chapter. By a chronologic arrangement, the historical advance in our knowledge of each phase of the subject is shown.

We take pleasure in acknowledging our deep gratitude to Dr. Henry Koplik, attending pediatrist to the Mount Sinai Hospital, who has generously permitted us to make extensive use of the valuable clinical material in his wards at the hospital. We are also greatly indebted to Dr. Julius Rudisch, Dr. Alfred Meyer, Dr. Nathan E. Brill, and Dr. Morris Manges, attending physicians at the Mount Sinai Hospital, for permission to use their clinical material.

Dr. H. F. L. Ziegel has kindly prepared the index.

We acknowledge with thanks the valuable assistance given us by Dr. John L. Kantor, interne at Mount Sinai Hospital, in the preparation of statistical matter.

We wish to thank Lea and Febiger for permission to reproduce plates from Dr. Koplik's book.

For the kind encouragement and valuable suggestions we are indebted to our publishers.

HENRY HEIMAN,
SAMUEL FELDSTEIN.

INTRODUCTION

THIS monograph is founded on a study of cases of meningococcus cerebrospinal meningitis which have been treated in my service in the children's wards of the Mount Sinai Hospital, New York, and reflects the methods of study of symptoms, diagnosis, and treatment in vogue there. I have been peculiarly fortunate in that the ages of the patients treated varied from earliest infancy to later childhood. A close study of these pages will show that we have been alive to every advance in pathology, methods of diagnosis, and treatment, and have applied the latter in a manner as to give a very definite idea as to their ultimate value. Though the Flexner serum is a most powerful weapon against this affection when properly applied, much remains to be done to deprive the disease of its terrors. This is particularly true of the infection as we see it in infants of tender age below one year.

The mortality in these patients is still not only high, but the maiming effects of the disease on the integrity of the general nervous system are too apparent. The general physician needs in his daily work every aid to the study of symptoms, their

differentiation and grouping, and an exposition of the safest methods of diagnosis and treatment. It is the object of such a monograph as this to give this aid and thus accomplish a useful mission.

HENRY KOPLIK, M.D.,
Chief of Service.

NEW YORK, October 1, 1913.

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MENINGOCOCCUS MENINGITIS

CHAPTER I

Introduction

Definition.—Meningococcus meningitis is an infectious, slightly contagious disease, which occurs sporadically and in epidemics, due to the presence, in the meninges of the brain and spinal cord, of the meningococcus (diplococcus intracellularis meningitidis), and characterized by a number of constitutional and local symptoms of great variability and irregularity.

Terminology.—In the extensive literature the disease has received a great number of names, such as spotted fever, spotted typhus, black fever, exanthematic typhus, brain fever, petechial fever, epidemic cephalalgia, and cerebrospinal fever. The term most commonly employed is that of epidemic cerebrospinal meningitis. But its inadequacy becomes evident when we consider the great number of sporadic cases which are seen in all the large cities. The specific nature of the disease having become firmly established, an etiologic designation is the only adequate

and proper term. It includes all forms and excludes none.

It is probable that epidemics of meningitis may also be caused by the pneumococcus and the streptococcus mucosus (Bonomé), but it is safe to say that the vast majority of epidemics recorded in the literature have resulted from infection by the meningococcus.

History.—The dim history of this disease begins in the Middle Ages. Many epidemics are mentioned in the literature in which symptoms very suggestive of meningitis were present. But, as autopsies were rarely performed, it is impossible to be certain that the disease was meningitis. They were described under phrenitis, petechial fever, cerebral fever, and epidemic cephalalgia.

The accepted history of meningococcus meningitis begins at Geneva in 1805. The epidemic started in February on the left bank of Lake Geneva, and lasted during March and April. Thirty-three persons died of the disease, but there were no cases of contagion at the hospital, and the commission appointed by the Government did not consider it deserving of being called an epidemic. The disease was described as follows by Vieusseux (quoted from Netter and Debré):

" It began suddenly with extreme prostration; the

face was drawn; the pulse feeble, small, and frequent, sometimes it could hardly be felt; hard and bounding in a small number of cases. There was violent headache, especially frontal. Then there appeared precordial pain or vomiting of bilious matter, rigidity of the spine, and convulsions in infants. . . . The body presented livid spots, especially after death, sometimes even during life."

The pathological description was given as follows by Mathey:

" The meningeal vessels were markedly congested. A gelatinous blood-stained fluid covered the whole surface of the brain. There was fluid in the ventricles. The choroid plexus was a deep red. A yellow puriform exudate was seen on the posterior aspect of the cerebral lobes and in the interior. There was no manifest change in the cerebral tissue. The same exudate was found along the optic nerves, the base of the cerebellum, and the vertebral canal."

In the United States the disease was first seen in epidemic form in Medfield, Mass., during March, 1806. It was described by Danielson and Mann in a contribution to the *Medical and Agricultural Register,* bearing the title, " A Singular and Very Fatal Disease which Lately made its Appearance in Medfield, Mass." On account of the remarkable descrip-

tion of the disease given by these authors, a part of the paper is worth quoting:

"Without any apparent predisposition, the patient is suddenly taken with violent pain in the head and stomach, succeeded by cold chills and followed by nausea and vomiting; matter discharged from stomach of no unusual or morbid appearance; respiration short and laborious . . . the eyes have a wild vacant stare without much, if any, appearance of inflammation . . . these symptoms are accompanied by a peculiar fearfulness, as if in danger of falling from the bed or the nurse's arms, and continue from six to nine hours, when coma commences, with increasing debility; extremities become cold; livid spots resembling petechiæ appear under the skin, on the face, neck, and extremities; pulse small, irregular, and unequal; spasms occur at intervals, which increase in violence and frequency in proportion as the force of the circulation decreases; at this time the eyes appear glassy, and the size of the pupils varies suddenly, from almost obliterating the iris down to the size of a millet-seed, and then again as suddenly dilating. These symptoms seem to mark the second period of the disease and continue from three to five hours. The third and last stage is distinguished by a total loss of pulsation at the wrists; livid appearances become more general; spasms more violent;

coma more profound; death! The patient has, in general, continued in the last stage from six to twelve hours."

On post-mortem examination, serous effusion was found between the membranes, which adhered to each other and to the brain in several places; congestion and softening of the brain.

The best and most classical history of the disease is given by Hirsch in his well-known treatise on "Historisch-Geographische Pathologie," to which the reader interested in this phase of the subject is referred. He divides its history into four periods:

1. 1805–1830, during which the disease was general in the United States. In Europe it occurred in isolated epidemics.

2. 1837–1850. During this period there were wide-spread epidemics in France, Italy, Algiers, the United States, and Denmark.

3. 1854–1875. In this period the disease was widely diffused throughout most of Europe, the adjoining countries of Western Asia, the United States, and parts of Africa and South America.

4. 1876–1882. During this period there were isolated epidemic outbreaks. We may add a fifth and sixth period,—from 1893 to 1903, and from 1904 to the present time. In these periods there were exten-

sive epidemics in the United States, Portugal, Germany, England, and France.

The following brief historical account is based on the studies of Hirsch and Jacobi.

The First Period (1805–1830).—During the first period the disease was epidemic not only in Medfield but also in New Hampshire, Connecticut, New Jersey, Vermont, Virginia, Kentucky, Ohio, New York, Pennsylvania, and Maine. From 1814 to 1816 epidemics occurred in all the New England States. From 1816 to 1823 no severe epidemics were observed. In 1823 there was an epidemic outbreak in Middletown, Conn. The epidemic in Trumbull, Ohio, in 1828, closed the first period in the United States. Three important contributions to the American literature of the disease were made in this period: the paper by Danielson and Mann, already mentioned; the communication by a committee of the Massachusetts Medical Society (consisting of James Jackson, Thomas Welch, and J. C. Warren); and the classical book by Elisha North entitled, "A Treatise on a Malignant Epidemic Commonly Called Spotted Fever." The epidemics were characterized by various eruptions and by the occurrence of pulmonary complications.

In Europe the disease prevailed in Brianca, Danzig, Brest, Paris, and Metz. The frequency of erup-

tions and respiratory complications was noted here also.

The Second Period (1837–1850).—In the United States the disease was wide-spread from 1842 to 1850. In 1842 Rutherford County, Tennessee, and Montgomery, Alabama, were visited by the epidemic. In 1845 an epidemic occurred in Mt. Vernon, Illinois. It prevailed in Arkansas, Vicksburg, Mississippi, Tennessee, and Missouri in 1846–1847. Montgomery, Alabama, was visited for the second time in 1848. In the same year the disease prevailed in Pennsylvania and Worcester, Mass. The negro quarters of New Orleans were invaded in 1850.

In Europe the most wide-spread epidemic during this period occurred in France. It began in the south of France and spread for the next ten years from the southwest to the northeast. By the movements of the 18th Regiment the disease was carried from the Landes to Rochefort, Versailles, Chartres, Metz, Nancy, Strassburg, Schlestadt, and Colmar. It affected chiefly the military population. The epidemic was transported to Algeria and Italy. From 1839 to 1845 wide-spread epidemics occurred in Italy. Epidemics were also seen in Corfu, Gibraltar, Denmark, and Ireland. In this period the clinical features of the disease were carefully studied and de-

scribed by the French clinicians (Lespes, Tourdes and Faure-Villars, etc.).

The Third Period (1854–1875).—In the United States there was subsidence of the disease from 1850 to 1856. Then new outbreaks occurred during 1856 and 1857 in Salisbury, North Carolina, and the western part of New York State. The disease prevailed in the Army of the Potomac in the winter of 1861–1862. In 1862–1863 it invaded the army camp around Newbern, N. C. It reappeared in Massachusetts in 1864–1865. Philadelphia had an epidemic in 1863–1866. During the same period it was prevalent in Indiana and Iowa, among the Confederate troops at Norfolk, Va., at the military school in Newport, R. I., Mobile, Alabama, Illinois, New Jersey, Vermont, Connecticut, and Ohio. In 1869–1870 meningococcus meningitis was seen in Alabama, Pennsylvania, New Jersey, New York City and Brooklyn, Illinois, South Carolina, and the port of Georgia. Massachusetts, Indiana, and Michigan were visited by epidemics in 1873. In Boston the epidemic occurred in 1874.

From 1854 to 1861 extensive epidemics occurred throughout the whole of the Scandinavian Peninsula, affecting Sweden more severely than Norway. The disease advanced from the south to the northwest, beginning each winter where it had stopped the previ-

ous summer. It caused 4158 deaths in seven years. Southern and central Germany was invaded during 1863–1866. Epidemics were also seen at this time in Austria, Hungary, and Russia. The disease was epidemic in Ireland from 1865 to 1868.

The Fourth Period (1876–1882.—In this period no very extensive epidemics are recorded, but the disease prevailed in the form of localized epidemics in France, Italy, Germany, Austria, and Scandinavia. There are no records of epidemics in the United States.

The Fifth Period (1893–1903).—In 1893 an extensive epidemic occurred in New York City, which was described by Berg. In the same year the disease appeared in the Lonaconing Valley in Maryland, and was carefully studied by Flexner and Barker. The epidemic in Massachusetts during 1897–1898 gave rise to the admirable contribution by Councilman, Mallory and Wright.

During this period epidemics were seen in France, Germany, Austria, Norway, Scotland, Ireland, Bosnia, Italy, and Algeria. The severe epidemic in Portugal during 1901–1903 gave rise to a valuable contribution by Bettencourt and França. In this period the bacteriology of the disease became established on a firm basis.

The Sixth Period (1904–).—The disease

prevailed in New York during 1904 and 1905. In 1905 there were 2755 cases. There was a severe epidemic in Prussia from 1905 to 1907. The provinces chiefly affected were Silesia and Westphalia. In Great Britain severe epidemics were present in Glasgow, Edinburgh, and Belfast. During 1908–1910 an extensive epidemic was seen in France. During 1910 a severe epidemic occurred along the Pacific Coast. In 1911 the disease spread to the Southwestern States, affecting chiefly Texas and Louisiana.

The extensive researches undertaken during this period have shown the importance of the germ carriers in the spread of the disease. In this period the culmination of the practical study of the disease was reached when the serum treatment was developed.

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CHAPTER II

Bacteriology

History.—In 1884 Marchiafava and Celli found at autopsy, in two cases of epidemic meningitis, oval micrococci within the protoplasm of leucocytes and endothelial cells. As no cultures were made, and the result of staining by Gram method is not mentioned, it can only be surmised, but not proved, that these observers were dealing with the meningococcus. Leichtenstern, in 1885, during an epidemic at Cologne, comprising 41 cases, saw, on microscopic examination of 9 cases, intracellular diplococci, cultures of which yielded a number of bacilli, and cocci which, although of the same shape, varied markedly in size. Schwabach, as quoted by Councilman, Mallory and Wright, also found diplococci in the pus-cells of the discharge from the ear in a case of otitis media secondary to meningitis. Previous to this time the only identifiable organism found in the meningeal exudate was the diplococcus pneumoniæ. Practically all authors of this period, including Weichselbaum, were of the opinion that the pneumococcus was the only organism capable of producing a primary meningitis.

In 1887, however, Weichselbaum found, in the

meningeal exudate and ventricular fluid of 6 out of 8 cases of primary apparently sporadic cases of meningitis, an organism clearly not the pneumococcus and which he named diplococcus intracellularis meningitidis. It was a Gram-negative diplococcus occurring partly within and partly outside the pus-cells. Culturally it was shown to be an obligatory aërobe, whose optimum growth temperature was 37° C. It grew best on media containing animal proteids and required transplantation every day or second day. It possessed feeble pathogenic powers, but direct inoculation in the meninges of dogs produced meningitis and encephalitis. Since in the other two of the eight cases Weichselbaum found the pneumococcus, he expressed the guarded opinion that both of these organisms might produce a primary meningitis. Moreover, as at that time, to his knowledge, there was no epidemic of meningitis in Vienna, he did not feel justified in claiming an important rôle for this diplococcus in the causation of *epidemic* meningitis.

Though his painstaking studies were confirmed by Goldschmidt in the same year and by Edler soon thereafter, the discovery aroused but slight interest and was soon almost wholly forgotten.

Isolated finding of the meningococcus was reported now and then. Weichselbaum, however, despite un-

remitting search, did not meet with this organism again until 1895. By this time the clinical study of meningitis had been immeasurably advanced by Quincke's announcement in 1891 of his method of obtaining cerebrospinal fluid in the living by lumbar puncture.

In 1895 Jaeger, while studying a small epidemic at a garrison in Stuttgart, found in 14 cases at autopsy an organism which he identified with the Weichselbaum diplococcus. It was partly intracellular, being found at times within the nuclei. While Gram-negative in sections, it stained by Gram in the exudates and cultures. It grew well on agar, glycerin agar, and bouillon at temperatures ranging between 22° and 37° C., and showed considerable resistance to external influences. Chains of from twenty to thirty individuals were seen in two cultures. At times a capsule was demonstrable. Despite the obvious morphologic and cultural differences between this organism and the diplococcus described so carefully by Weichselbaum, Jaeger identified the two, and claimed that this diplococcus, and not the pneumococcus, as had been generally accepted up to this time, was the sole infective agent of epidemic cerebrospinal meningitis. His publication, unlike that of Weichselbaum, aroused great interest, and in the suc-

ceeding years many apparent confirmations of his observation were reported.

Heubner, in 1896, found, in the lumbar-puncture fluid of two cases, a diplococcus which presented all the characteristics described by Weichselbaum. In three other cases, however, he demonstrated the presence of a Gram-positive diplococcus which formed chains and grew at room temperature. By injecting this organism in the spinal canal of a goat, he produced acute meningitis.

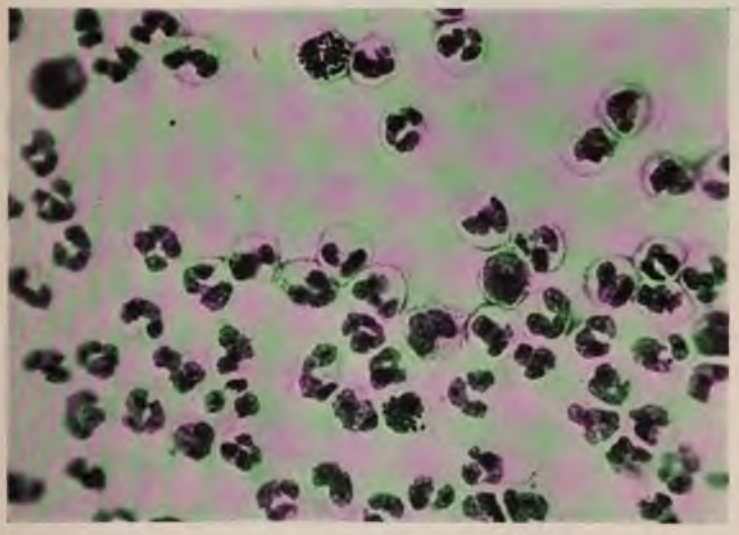
A period of great confusion followed. Some confirmed Weichselbaum's observations, others those of Jaeger, while still others attempted to identify the meningococcus with the pneumococcus. Soon thereafter the view became quite prevalent that there were two types of the meningococcus, the Weichselbaum type and the Jaeger-Heubner type. Considerable light was thrown on this phase of the meningitis question by the extensive studies of Councilman, Mallory and Wright (111 cases, 55 lumbar punctures, and 35 autopsies), Faber (60 cases), Albrecht and Ghon (30 cases), and Bettencourt and França (271 cases). The more recent studies during the large epidemics in Germany, America, England, and France, aided as they were by the development of the fermentation test and the modern serum reactions, have shown conclusively the untenability of the contentions of

Jaeger and his followers, and completely established the constancy of those characteristics of the organism originally described by Weichselbaum. An explanation for the strange results obtained by the Jaeger school was found in the difficulties surrounding the growth of the meningococcus on artificial media and the ease with which other organisms that grow under less exacting conditions contaminate the media employed for its cultivation. In animal experiments the ready invasion of more resistant secondary microorganisms was another frequent source of error. By his studies of the morphological, cultural, fermentative, and agglutinating properties of the two diplococci, v. Lingelsheim has shown that they can not be considered to belong to the same species. To avoid confusion in the future, he prefers to call the Jaeger coccus, diplococcus crassus.

The following account of the bacteriologic features of the meningococcus is based in part on the admirable paper of Elser and Huntoon.

Staining.—All the ordinary aniline dyes stain the meningococcus with great ease. It is now well established that the meningococcus is invariably Gram-negative, *i.e.*, it takes the counterstain. This staining characteristic of the meningococcus is of great diagnostic importance, as it offers a quick and reliable method of identification of this organism in the cere-

A



B

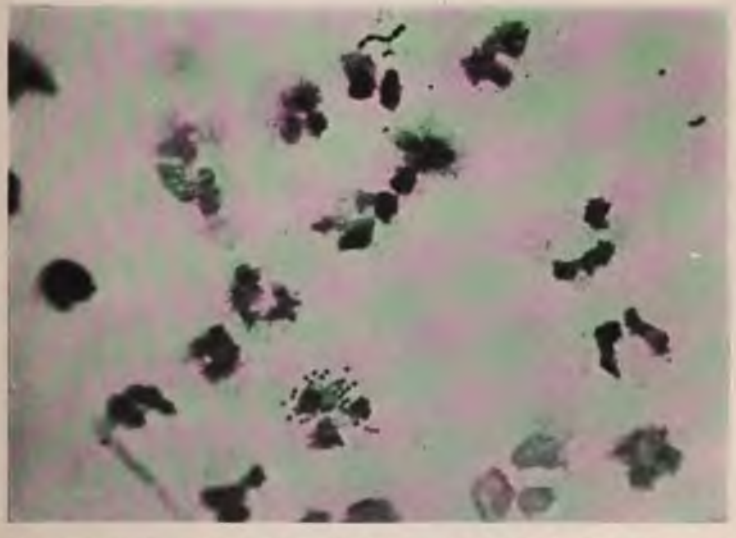


FIG. 1.—*A*, cerebrospinal exudate. Diplococcus intracellularis. *B*, cerebrospinal exudate mixed infection: diplococcus intracellularis and streptococcus.

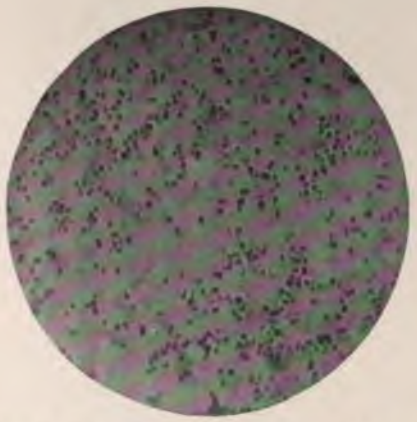


FIG. 2.—Pure culture of meningococcus 18 hours old. Glucose ascitic agar.

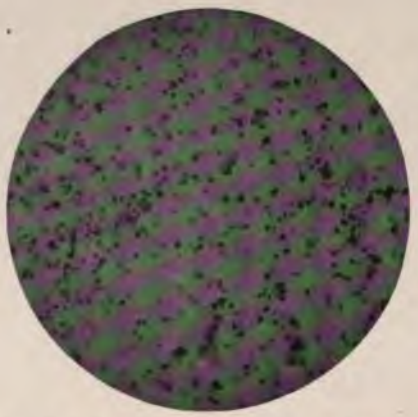


FIG. 3.—Pure culture of meningococcus 48 hours old. Glucose ascitic agar.

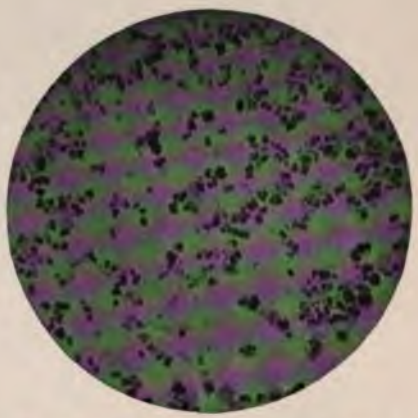


FIG. 4.—Pure culture of meningococcus 72 hours old. Glucose ascitic agar.

brospinal fluid. The Neisser stain frequently shows the presence of metachromatic granules which are microchemically identical with the Babes-Ernst bodies. The number and size of these granules vary with the strain of the organism, its age, and the culture-medium on which it grows. When grown on glucose ascitic agar at 36° C., the granules begin to appear after six hours, and attain their maximum size within eighteen hours. They disappear completely after a short exposure to room temperature, or after more than a week's growth on an artificial medium.

Morphology (Fig. 1).—The typical form of the meningococcus is that of two hemi-ellipses apposed by their flat surfaces and separated from each other by a linear space. While the double coccus is the predominant form, tetrads and small groups of diplococci are not infrequent. Isolated single cocci occur more rarely. The meningococcus shows no distinct capsule. At times a mucinous envelope is seen, which has been mistaken by some observers for a capsule. It may also be surrounded by an unstained zone which is due to contraction of the cell envelope or retraction of the culture-medium.

In the exudate obtained by lumbar puncture, the diplococci are often found within the protoplasm of the leucocytes. At times these are completely filled

with meningococci. The relative number of intra- and extracellular organisms varies with different specimens of cerebrospinal exudate, and seems partly dependent on a difference in the strains of the organism. Following the injection of serum, the organisms, if at all demonstrable, are very frequently confined to the protoplasm of the leucocytes. The phagocytic cells may be normal or degenerated.

Lack of uniformity as regards size, shape, and staining is a striking characteristic of this organism. Polymorphism is usually marked in smears from the nasopharynx and still more in those derived from cultures. In vigorous young cultures (sixteen to twenty-four hours old) most of the organisms stain sharply and uniformly. In cultures twenty-four to forty-eight hours old, four forms are seen:

1. Predominantly well-stained diplococci and tetrads.

2. Intensely stained cocci, normal in size and shape (resistant forms).

3. Less deeply stained normal cocci.

4. Intensely stained giant forms which are from four to five times as large as the ordinary cocci (Figs. 2, 3, and 4). The last two are involution or degeneration forms. These disappear rapidly in older cultures. As degeneration progresses, the cocci first

fail to stain, later they become disintegrated, and finally unstained detritus alone is left.

Flexner has shown that this process is due to the action of an enzyme, which is present in the cell bodies of the meningococci. Soon after the death of the organism the enzyme begins to dissolve the cell envelope. When the meningococcus is killed at 60° C., disintegration proceeds rapidly, as the enzyme is not affected by this temperature. Killed at 65° to 70° C. there is no disintegration, as the enzyme is also destroyed by this temperature. A similar action is exhibited by potassium cyanide, which kills the organisms and also inhibits the action of the enzyme. This enzyme is also capable of disintegrating other germs such as bacillus coli, typhoid bacillus, pyocyaneus, staphylococcus, and micrococcus catarrhalis. The meningococcus never occurs in long chains. This is another important characteristic that separates it from the Jaeger coccus. Even short chains of four to six individuals are very rarely seen. The presence of chains in a culture is therefore presumptive evidence that the organism in question is not the true meningococcus.

Cultural Characteristics.—The meningococcus is one of the most difficult organisms to grow on artificial media. It makes exacting demands as regards the composition and reaction of the medium, the

degree of temperature, and the humidity. It dies readily in the cerebrospinal fluid soon after its removal from the body. After eighteen hours, as a rule, such fluid no longer yields viable organisms. Successful cultures from cerebrospinal fluid demand the use of considerable quantities (several cubic centimetres) of this fluid. In autopsy material the death of the meningococcus is even more rapid. Distant transportation of such material is therefore to be avoided in cultural studies.

When first isolated from the body, the meningococcus will not grow on a medium that does not contain animal proteid. Ascitic agar (ascitic fluid one part, 2 per cent. plain or glucose agar two parts) has been found by the greater number of observers to be the most suitable culture-medium for the meningococcus. It also grows well on pleuritic agar, sheep serum agar, blood agar, ascitic bouillon, and Loeffler's serum. At first it requires daily transplantation on these media. After four or five generations transplantation once a week is sufficient. Grown for some time on these media most of the meningococcus strains can thereafter live on plain glucose agar. Sudden, unexpected death of the organism is not a rare phenomenon. The medium should be neutral or slightly acid (+ 0.8 to phenolphthalein, Elser and Huntoon). The optimum temperature is 36.5° to 37° C.

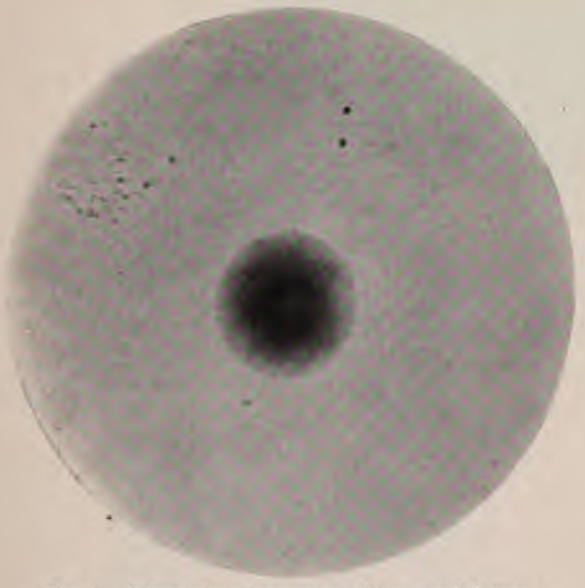


FIG. 5.—Colony of meningococcus. Glucose ascitic agar.

FIG. 6.—Plate culture of meningococcus. Glucose ascitic agar.

FIG. 7.—Slant culture of meningococcus. Glucose ascitic agar.

Growth on Ascitic Agar Plates (Figs. 5 and 6). —At the end of twenty-four hours' growth the plate shows small, transparent, glistening, round disks which are slightly raised and have a moist surface. The diameter of the colonies is about one to three millimetres. By reflected light they appear gray or grayish-white. By transmitted light some colonies are gray and uniformly translucent, others have a semi-opaque, grayish-white or faintly yellow centre surrounded by a transparent peripheral zone, while others show several zones of varying opacity. Seen through a low-power lens, the colonies appear as faintly yellow disks, having well-defined borders which are smooth or slightly irregular.

At the end of forty-eight hours, the colonies show slight increase in size, the diameter being three to four millimetres. The surface is more elevated, and has a glistening homogeneous appearance. The colonies are moderately viscous, not adherent to the medium, and form a uniform suspension when shaken in salt solution. A loopful of the growth is grayish-white in color, while larger masses have a pinkish tint when added to a colorless medium.

At the end of seventy-two hours crystalline deposits have been observed by Albrecht and Ghon, Bettencourt and França, and Elser and Huntoon. They are, however, present in cultures of other Gram-

negative diplococci. At this time the centre becomes less transparent and shows a distinctly brownish tint.

Growth on Ascitic Agar Slants (Fig. 7).—The most abundant growth is usually seen in the vicinity of the water of condensation, where the moisture favors the growth of the meningococcus. Discrete colonies of varying size and opacity are seen. The water of condensation presents a diffuse turbidity, and a sediment of cocci collects at the bottom of the tube. A pellicle may appear on the surface. Trautmann and Elser and Huntoon have seen at times a more or less distinct greenish-yellow discoloration of the medium after several days' growth. This pigment was soluble in distilled water and was confined to the medium. The presence of glucose favored its occurrence. Its nature was not determined. In very old cultures a brownish discoloration of the medium is frequently observed.

Growth on Blood Agar.—The meningococcus shows a very viscid growth of a milky, sometimes faintly violet or greenish tint. It is more opaque and less glistening than on ascitic agar.

Growth on Ascitic Broth.—When not disturbed a delicate pellicle is formed on the surface of the broth. The medium shows a diffuse turbidity, and a sediment collects on the bottom of the flask.

Growth on potato is feeble and hardly perceptible.

Growth in milk is very slight. There is no coagulation.

Conditions Affecting the Viability of the Meningococcus.—The meningococcus is very sensitive to changes in humidity and temperature. It suffers marked reduction in viability when exposed to direct sunlight. This lack of resistance, as we shall see later, has an important bearing on the mode of dissemination of this organism. The greater resistance of the diplococcus found by Jaeger, which, as we stated above, he identified with the meningococcus, led him and others to draw far-reaching but erroneous conclusions regarding the mode of contagion in this form of meningitis. All those who have dealt with pure cultures of the meningococcus have reached practical unanimity as regards the susceptibility of this organism to external influences.

Effect of Desiccation.—Cultures in which proper precautions are not taken to prevent drying die within two to three days. Sealed properly the organisms survive more than fourteen days. Exposed on porous material, such as filter-paper or linen, they lose their vitality in six hours at a temperature of 37° C., in twelve hours at room temperature. Forty-eight hour cultures are more resistant than older or younger cultures.

Effect of Light.—In diffuse sunlight, at room

temperature, the meningococcus survives for five to seven days in cultures. After eight days all cultures are killed. The effect of direct sunlight varies somewhat with the climate and season of the year.

Bettencourt and França, in Portugal, found that the meningococcus was killed after two hours' exposure to direct sunlight. In Berlin, during June, v. Lingelsheim found no living organisms after four to five hours' exposure, whereas Kutscher, in the same city, during March, found eight to twelve hours' exposure necessary. Elser and Huntoon, in New York, conducting their experiments during the month of August, found living cultures after eight and nine hours' exposure.

Effect of Temperature.—The meningococcus does not grow below 25° or above 43° C. Some strains fail to grow above 41°. Between 25° and 31° C. it shows but feeble growth. In the ice-box (8° C.) it may survive from four to six days. At 10° to 20° C. it is killed in two hours. At 25° to 26° C. in a dark room, Elser and Huntoon found living strains on glucose agar at the end of three, four, or five weeks. v. Lingelsheim found exposure to room temperature fatal to the meningococcus in five days.

Effect of Moist Heat.—No living organisms were found by v. Lingelsheim when emulsions were exposed to 50° C. for one hour, and 60° C. for ten min-

utes, 70° C. for five minutes, 80° C. for two minutes. Elser and Huntoon found that a temperature of 45° C. moist heat was resisted for three hours, while 55° C. was resisted by some strains for two hours. Bettencourt and França found a much greater susceptibility to moist heat.

Effect of Disinfectant Solutions.—This table, based on Flügge's experiments, shows the effects of various disinfectants on the meningococcus.

3 per cent. hydrogen peroxide 1/10 per cent. to 1 per cent. corrosive sublimate 1 per cent. silver nitrate 1 per cent. to 2 per cent. carbolic acid 1 per cent. lysol 10 per cent. menthol	kills the meningococcus in 1 minute.
1 per cent. sulphuric acid 2 per cent. protargol 70 per cent. alcohol	kills the meningococcus in 2 minutes.
1 per cent. lye	kills the meningococcus in 7 minutes.
1 per cent. hydrogen peroxide ½ per cent. protargol	kills the meningococcus in 9 minutes.

Dopter and Koch found that when essence of eucalyptus, bergamot, origanum, and peppermint,

ether, xylol, and formol were added to a culture, growth was inhibited. Koch found that five to fifteen drops of pyocyanase added to a bouillon culture prevented the growth of the meningococcus, whereas one cubic centimetre of pyocyanase added to an ascitic-agar tube retarded growth but slightly. A thick emulsion of meningococci in pyocyanase showed growth when added to bouillon after one-half hour but not after three hours.

Fermentation of Carbohydrates.—v. Lingelsheim was the first investigator to demonstrate that the meningococcus ferments only dextrose and maltose. By the addition of litmus to a culture-medium, the formation of acid is readily shown. Buchanan, Dunn and Gordon, and Andrewes claimed fermentative action on galactose, while Arkwright and Andrewes found that not only was galactose fermented but also levulose. Their apparently contradictory results have been shown by Elser and Huntoon to be due to the fact that these sugars when heated in the presence of alkali undergo cleavage into dextrose. To obviate this important source of error, they advise the separate sterilization of the sugar dissolved in distilled water in old Jena glassware which has been steamed for several hours so as to reduce to a minimum the amount of alkali given off by the glass. Fermentation by the meningococcus of dextrin as found by

Andrewes is probably attributable to the presence of impurities. Maquenne has shown that so-called chemically pure dextrin contains small quantities of maltose, isomaltose, or dextrose. According to v. Lingelsheim and Elser and Huntoon, it is advisable to use solid media for determination of fermentative action. The discordant results previously obtained are partly attributed by these observers to the use of liquid media. Not only do these media show a tardy reaction, but the organism may fail to grow in them. Moreover, a microscopic examination, which should always be made to determine the purity of the growth, is carried out more readily when solid media are employed.

Agglutination Reaction.—In 1901 Albrecht and Ghon demonstrated the presence of specific agglutinins in the sera of animals repeatedly injected with cultures of the meningococcus. Jaeger undertook a systematic investigation of this property of the serum in rabbits. He apparently proved the identity of his diplococcus with the Weichselbaum meningococcus by showing that rabbits injected with either organism yielded sera which agglutinated both of them. These results Bettencourt and França failed to confirm in the horse. v. Lingelsheim found that, while meningococcus immune sera (derived from the rabbit) agglutinated the diplococcus crassus (Jaeger

diplococcus), immune sera of animals injected with diplococcus crassus failed to agglutinate the meningococcus. Jochmann confirmed the observations of Bettencourt and França and showed that there was no agglutination relationship between the two organisms.

In carrying out agglutination tests it is important to have controls in salt solution and normal sera. The macroscopic reaction is more reliable than the microscopic. The technique of Elser and Huntoon is as follows: Homogeneous suspensions are made in normal salt solution containing the same quantity of moist bacteria. Equal amounts of this suspension are thoroughly shaken in test-tubes containing a graded series of diluted sera. These are kept in the incubator for two hours, then placed in the ice-box for twenty-two hours. Readings are made at one, two, three, four, and twenty-four hour intervals. In most cases it is not necessary to go beyond twenty-four hours. A positive agglutination is shown by the presence of clumped cocci at the bottom. The supernatant fluid shows a slight degree of uniform turbidity. The immune sera may be the polyvalent sera now employed for treatment, or special sera derived from animals that have been injected intravenously with increasing doses of killed meningococci.

The meningococcus shows variable agglutinating

activity, the same strain often varying markedly from day to day. Elser and Huntoon found incomplete or absent agglutination in 40 per cent. of 65 strains (1–100). Killed cultures usually give more uniform results. Kutscher advocates testing cultures at the temperature of 55° C. In this manner he obtained positive results with cultures that were previously negative at 37° C. Owing to the presence of group agglutinins, it is often difficult to separate by this test the meningococcus from other related organisms. Not infrequently, for example, the gonococcus yields positive results with meningococcus immune sera at dilutions which do not agglutinate with the meningococcus. To obviate this difficulty absorption tests are employed.

Absorption Tests.—These tests depend upon the well-known fact that specific agglutinins are absorbed only by bacteria which belong to the same species as those employed for the production of the immune serum. The experiment is carried out by adding a suspension of the meningococcus to an immune serum which is placed in the incubator for 2 hours and then centrifugalized. Subsequent addition of the same or another strain of the meningococcus to this exhausted serum shows that it has lost a large part of its agglutinating power. This loss is greater with the more agglutinable strains, but there is no definite

relationship between absorptive capacities and agglutinability. The experiments of Dunham seem to prove that when filtration proceeds slowly a considerable loss of agglutinability results. It is therefore advisable to use centrifugalization in doing absorption tests. These tests show that there is no group relationship between the meningococcus and the Jaeger coccus.

Precipitin Reaction.—The presence of meningococcus precipitins was shown by Bruckner and Christéanu and Dopter and Koch. A variable quantity of antimeningitis serum (one to two drops) is added to from twenty to fifty drops of an aqueous extract or autolysate of the meningococcus, and is then incubated for twenty-four hours. A positive reaction is shown by the formation of a precipitate.

Complement Fixation Reaction.—This reaction is more specific than either the agglutination or precipitin reaction, as the fixation of complement in an immune serum occurs only with the homologous antigen.

Action of Bile Salts.—Ficker has shown that a suspension of a meningococcus culture becomes clear on addition of a solution of bile salts. The gonococcus, however, yields the same reaction. The test is carried out as follows:

To 0.5 cubic centimetre of an emulsion of a twenty-four-hour old bouillon culture (one loopful

to one cubic centimetre of physiological salt solution) add 0.1 cubic centimetre of a fresh 20 per cent. aqueous solution of sodium taurocholate. The mixture becomes clear immediately or after one hour's incubation at 37° C.

Peritoneal Reaction.—This was first demonstrated by Dopter, and is based upon the Pfeiffer phenomenon. One cubic centimetre of an unheated antimeningitis serum is injected in the peritoneal cavity of a young guinea-pig (250 grams). Exactly twenty-four hours later, one-sixth of a meningococcus culture is injected intraperitoneally. The peritoneal exudate within twenty to thirty minutes shows few or no free meningococci. Dopter considers this test specific, as it serves to differentiate the meningococcus not only from the pseudomeningococci, but also from the parameningococcus.

Intravenous Reaction (Epreuve de la Veine).—Briot and Dopter have shown that when a young guinea-pig is injected intravenously with a mixture of unheated antimeningitis serum and an emulsion of a meningococcus culture, there appear within a few minutes convulsions, muscular contractures, dyspnœa, coma, and death. This reaction occurs with the meningococcus only, and is due either to a peptotoxin or the bacteriolytic action of the serum. The occasionally severe symptoms which develop in horses

in the course of immunization are probably of the same nature.

Pathogenicity.—The meningococcus shows feeble and variable pathogenic action on the usual laboratory animals. Subcutaneous injections are usually without effect. Young guinea-pigs (weight 175 to 200 grams) and white mice are the most susceptible animals.

Action on Guinea-Pigs.—Intraperitoneal injection in guinea-pigs produces death in from two to five days. There is marked reduction in temperature. The animal crouches in a corner with hair erect. The abdominal muscles are tense, and the abdomen becomes distended with gas. If death occurs in less than eighteen hours, the exudate is scanty and poor in leucocytes. If the animal dies in from twenty-four to thirty-six hours, more characteristic lesions are seen. There is an abundant free, thick, viscid, yellow exudate, especially on the anterior surface of the liver and rolled-up omentum. The parietal and visceral peritoneum shows injection of its vessels and small hemorrhages. The spleen is congested and somewhat increased in size. There is gelatinous œdema of the pancreas and pancreatic tissue. The adrenals show congestion and small hemorrhagic foci. There is an increase of clear fluid in the pleural cavity. Meningococci are found in variable quantity in the

peritoneal exudate, free and in the leucocytes. They may also be present in the heart's blood and in the spleen. If the animal survives for five to six days, peritoneal exudate is absent and meningococci are not demonstrable. Similar lesions are found in white mice.

Although meningococci have been found in the blood and abdominal viscera, indicating a general invasion, it is probable that the lesions above described are due to an intoxication rather than infection, since similar lesions have been produced by the injection of dead meningococci and autolysate. Elser and Huntoon were able to recover the meningococcus from the blood within five minutes of an intraperitoneal injection of a culture, at a time when multiplication of the organism was out of the question.

Action on Rabbits.—Intravenous injection does not produce acute symptoms. The animals usually die of emaciation. Hemorrhages in the mucous membrane of the gastro-intestinal tract have been found by Elser and Huntoon. These lesions favor the passage of other organisms from the intestinal tract, as shown by feeding experiments with typhoid bacilli.

Action on Dogs.—Suboccipital injection may lead to convulsions, paralysis, or coma. In one case a transient meningitis was produced.

Action on Goats.—Councilman, Mallory and Wright succeeded in producing a meningitis.

Action on Monkeys.—Successful results in this animal were obtained by v. Lingelsheim and Leuchs, Flexner, and Stuart McDonald by intraspinal injection of large doses. Before death, which usually occurred in from eighteen to twenty hours, the animals exhibited convulsions, nystagmus, dyspnœa, and hyperæsthesia. At autopsy there were found intense congestion and foci of extravasation in the brain and meninges. A thick exudate rich in leucocytes was found at the base of the brain. In the ventricles turbid fluid was present. Normal or degenerated meningococci were found within the leucocytes.

By injecting repeated small doses, Flexner succeeded in keeping the animals alive for several weeks. At death there were found acute and chronic lesions with abundant exudate rich in leucocytes. The spinal dura was deeply injected. The ventricle and central canal of the cord were dilated, and hydrocephalus was found in those cases where the foramen of Magendie was occluded. Although these lesions are very similar to those found in the natural disease in man, by themselves they do not prove the selective action of the meningococcus for the meninges, as similar inflammatory changes in the meninges of animals can be pro-

duced by intraspinal injections of a number of pyogenic bacteria.

Difference in Strains.—Since the introduction of specific serotherapy, the biologic differences between various strains of the meningococcus have received extended consideration. We have previously called attention to the marked variations in agglutinative capacity. Differences in absorptive capacity and in fixation of complement have also been demonstrated. Other differences are shown in the culturability, survival in cultures, and power to ferment carbohydrates. The most important differences, however, from a therapeutic stand-point, relate to variation in pathogenic power, degree of digestibility by leucocytes, and power to resist solution by immune serum. It is probable that some cases of meningitis which do not respond satisfactorily to the therapeutic action of the serum are due to infection by strains of the organism which are fast to the antiserum employed.

Gram-Negative Cocci in the Nasopharynx.—In the course of the numerous investigations on the presence of the meningococcus in the nasopharynx, a subject of supreme theoretical and practical importance, it was found that this region of the body constantly harbors a number of Gram-negative microorganisms which microscopically closely resemble the

meningococcus. Failure to take this fact into account renders most of the earlier studies on this phase of the subject of little value. As a result of the admirable work of v. Lingelsheim at the Beuthen Station, we are now in possession of a number of differential characteristics which enable us to identify and classify most of these organisms.

According to Elser and Huntoon, the following Gram-negative cocci may be found in the nasopharynx of man:

1. Meningococcus.
   (Parameningococcus-Dopter.)
2. Pseudomeningococcus, separable from the meningococcus only by absorption tests.
3. Micrococcus gonorrhœa (Neisser).
4. Micrococcus catarrhalis (R. Pfeiffer).
5. Micrococcus pharyngis siccus (v. Lingelsheim).
6. Chromogenic Gram-negative cocci:
   Group I. Ferments dextrose, maltose, levulose, and saccharose.
   Group II. Ferments dextrose, maltose, and levulose.
   Group III. Ferments dextrose and maltose.

Though included here in one group, there is no true kinship between these organisms with the exception of the meningococcus, pseudomeningococcus, and gonococcus, which possess common group agglutinins.

The diplococcus crassus (or Jaeger coccus) is not included in this list, as it is usually Gram-positive.

Though morphologically hardly distinguishable from one another, they possess individual cultural, fermentative, and agglutinating characteristics which are sufficiently well marked to enable us to separate them into distinct species. We are unable to enter here into a description of the character of the cultures of each member of the group. The reader is referred to the paper by Elser and Huntoon. With the exception of the pseudomeningococcus and gonococcus, the cultural appearance does not resemble that of the meningococcus. The pseudomeningococcus can be differentiated from the meningococcus only by the employment of absorption tests. The gonococcus, unlike the meningococcus, ferments only dextrose. The fermentative properties of the members of this group are given in the following table, from Elser and Huntoon:

Number of strains.	Dextrose.	Maltose.	Levulose.	Saccharose.	Lactose.	Galactose.	Dextrin.	Mannose.	Dulcite.	Inulin.
Meningococcus 200	+	+	0	0	0	0	0	0	0	0
Pseudomeningococcus 6	+	+	0	0	0	0	0	0	0	0
Gonococcus 15	+	0	0	0	0	0	0	0	0	0
Micrococcus catarrhalis 64	0	0	0	0	0	0	0	0	0	0
Micrococcus pharyngis siccus 2	+	+	+	+	0	0	0	0	0	0
Chromogenic—										
Group I 28	+	+	+	+	0	0	0	0	0	0
Group II 11	+	+	+	0	0	0	0	0	0	0
Group III 9	+	+	0	0	0	0	0	0	0	0
Jaeger micrococcus, Kral 1	+	+	+	+	+	+	0	0	0	0
Diplococcus crassus, Kral 1	+	+	+	+	+	+	0	0	0	0
Parameningococcus+	+	0	0	0	0	0	0	0	0	0

The agglutination reaction is another valuable means of identifying the members of this group. Unfortunately, its value is considerably reduced by the occurrence of many inagglutinable strains amongst the meningococci. Some investigators, basing their views on agglutination reactions, classify the meningococcus and gonococcus as two varieties of the same species. But it is rather strange that the selective actions on the tissues of the body are so different for the two organisms,—one for the meninges and the other for the mucous membrane of the genito-urinary tract and joints. Jundell and Zupnik failed to produce any reaction by inoculation of meningococcus culture on the urethra. On the other hand, with the exception of perhaps one, there are no reliable reports of the finding of gonococci in meningeal exudate. The few reports extant are faulty in that culture, fermentative, and absorption tests were not made.

Parameningococcus.—In 1909 Dopter found in the nasopharynx an organism which closely resembled the meningococcus, but which showed slight or no agglutination with antimeningitis serum. Subsequent studies by this observer demonstrated the fact that it possessed specific agglutinins and precipitins, and that with an antimeningococcus serum it failed to respond to his peritoneal and intravenous tests. Carnot

and Marie found this organism in the blood of a fatal case of malignant purpura, and Menetrier and Brodin first described a meningitis due to the parameningococcus. Since then more than a dozen such cases have been recorded by various French observers. In one case of Widal and Weissenbach no effect was seen from the use of antimeningococcus serum (Dopter). The subsequent application of an antiparameningococcus serum prepared by Dopter resulted in a cure.

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CHAPTER III

Epidemiology

The epidemiology of meningococcus meningitis presents features which are not often seen in other epidemic diseases. At times they have been so strange and puzzling and so different from the characteristics usually associated with a contagious disease that the contagiousness has been questioned by not a few observers. In periods of wide-spread epidemics it has usually been impossible to trace the progress of the contagion from one locality to another. As a rule, there is no regular progression or extension of the disease. It moves by leaps and bounds, and seems to strike at haphazard. Simultaneously affected localities are often separated by those that almost wholly escape the infection. The evolution of an epidemic is usually slow and gradual, and there is no regular cycle as observed in epidemics of other disease. The cases are scattered and seem to be grouped around several small foci instead of a single focus. Physicians and hospital attendants rarely contract the disease, while a multiplicity of cases in a family or dwelling is rather unusual and in certain epidemics has been entirely absent. Moreover, as compared with other epidemics, but a small propor-

tion of the population contracts the disease. This feature is especially noticeable in large cities, the morbidity rate from epidemic meningitis in the four large epidemics that occurred in New York City having been as follows:

1872	8.07 per 10,000
1881	3.70 per 10,000
1893	2.67 per 10,000
1904–1905	6.30 per 10,000

In smaller communities the relative number of cases may be much higher, as in

Lippisch (near Danzig)	1250 per 10,000
Aigue-Mortes, 1841	533 per 10,000
Strassburg, 1841	30 per 10,000

As a rule, the disease in large cities does not attack more than 1 to 2 per 10,000 of the population. This is a much smaller morbidity rate than that of measles, scarlet fever, diphtheria, pneumonia, or typhoid during periods free from epidemics of these diseases.

Contagiousness.—Despite the epidemiologic facts above stated, there can be little doubt regarding the contagiousness, feeble though it is, of this form of meningitis. Those clinicians who have denied it have based their conclusions on personal experience during a limited number of epidemics in which certain

features which we are accustomed to associate with a contagious disease were absent. It is not strange that Vieusseux, the first to recognize the disease as a clinical entity, held this opinion. In the epidemic at Geneva during the latter part of the year 1805, the disease, which began in the crowded quarters of the city, did not apparently extend from case to case. The attendants on the sick and their neighbors uniformly escaped infection. In those dwellings in which there was more than one case, the patients did not acquire the disease from one another, as it appeared not successively but simultaneously. Berg, in the New York epidemic of 1893, was unable to find amongst his patients a single instance in which more than one member of a family contracted the disease. In the epidemic of 1904–1905, however, he encountered a number of such instances.

Bearing in mind the feeble infective power of the meningococcus for the meninges, it becomes evident that a small number of undoubted instances of traceable contagion is infinitely more convincing than much negative evidence. The literature teems with many indubitable instances of direct contagion. Netter and Debré quote Sewall's observation during the New York epidemic of 1872 in which six members of the Brown family successively contracted the disease at intervals of from one to thirty-four days.

Peterson, as a result of a very thorough investigation of an epidemic in Berlin, succeeded in tracing direct contagion between thirty-four cases. Cholard reports the occurrence of three cases of meningitis in the family of a wood-cutter living in a completely isolated cabin in a forest of Braubourg. The outbreak occurred a few days after the return of the head of the family from the military manœuvres at Evreaux, where an epidemic was prevalent at the time. According to Bolduan and Goodwin, there were, among 1500 cases in the New York epidemic of 1904–1905, 88 instances of more than one case in a house, thus—

39 instances in which there were 2 cases in a house
15 instances in which there were 3 cases in a house
2 instances in which there were 4 cases in a house
1 instance in which there were 5 cases in a house
1 instance in which there were 8 cases in a house

In 34 instances the intervals between the appearance of the cases were as follows:

In 9 instances the interval was 4 days or less
In 5 instances the interval was 4–7 days
In 5 instances the interval was 1–2 weeks
In 4 instances the interval was 2–3 weeks
In 3 instances the interval was 3–4 weeks
In 2 instances the interval was 4–5 weeks
In 3 instances the interval was 5–6 weeks
In 2 instances the interval was 7–8 weeks
In 1 instance the interval was 3 months

In three instances the disease seems to have been communicated to or by the family of the janitors. School contagion seemed probable in two instances.

Contrasted with the many records of immunity from contagion in general hospitals, a fact which (as we shall see later) is attributable to the general absence of meningococcus carriers in these institutions, is the report by Leichtenstern of a small epidemic in the Cologne Hospital. Three nurses and a sister in attendance on cases of meningitis in the wards contracted the disease. Three of them had not left the hospital for some time and could not have acquired the disease from the outside. Montanari, likewise, reports the infection of a nurse and her two daughters in a hospital at Foggia. In the New York Hospital, Elser and Huntoon found three instances of infection of nurses in attendance on adult cases of meningitis. Cases of school contagion, though rare, are reported by Bolduan and Goodwin and Netter and Debré. The latter observed 10 cases, 6 of which attended a common school. Among 231 pupils of this school there were found 40 meningococcus carriers,—*i.e.*, 21.21 per cent.

A number of instances of the spread of an epidemic from one locality to another along the routes of travel are recorded in the literature. According to Netter and Debré, the progress of the French

epidemic of 1837–1850 from the southwest to the northeast is traceable to the movements of the 18th Regiment of the French army. The same authors attribute the Algerian epidemic of 1840 to the presence of a French garrison. The epidemic in Italy of the same period, which began in Ancône, is also attributable to intercourse with the French army.

In the literature, instances are recorded of the spread of an epidemic from an infected garrison to the civil population. In Strassburg, Schlestadt, and Metz the first cases in the civil community occurred in the streets adjoining the barracks. In Foggia the epidemic appeared after the arrival of a recruit from Viesto, where the disease existed the previous year.

Geographic Distribution.—Meningococcus meningitis shows the greatest prevalence in the north temperate zone. Epidemics, however, have been seen as far north as Iceland, and as far south as Java and Soudan. The historical sketch shows that no part of the civilized world has escaped its visitation. Northeastern United States, France, and Germany have shown special liability to epidemic outbreaks.

Seasonal Incidence.—Epidemics of meningitis usually begin in the winter and reach their maximum intensity in the spring months. Relatively few epidemics have been seen in the summer and autumn. Of 85 American epidemics recorded by Hirsch, 37

occurred in the winter, 18 in the winter and spring, and 23 in the spring. According to Aitken, 311 of 417 epidemics in Sweden occurred in the winter. In the Prussian epidemic during 1905 to 1908, the distribution of the cases was as follows:

	1905.	1906.	1907.	1908.	Total per cent.
December, January, February.....	531	580	466	353	18.2
March, April, May.....	2545	1031	1254	609	61.0
June, July, August.....	535	258	577	199	14.8
September, October, November.....	151	160	286	125	6.0

From these figures it can be seen that approximately 80 per cent. of the cases occurred in the winter and spring months. In New York in 1904 the epidemic began in March and reached its height in May; the next year it began in February and attained its maximum in March. While many of the reported epidemics have occurred in unusually severe winters, not a few have been seen in unusually mild weather, as at Metz in 1839–1840, Italy in 1839–1840, 1840–1841, Indiana in 1862–1863, Kentucky in 1866. The epidemic at Smyrna in 1868–1870 occurred during an excessively hot spring. No satisfactory explanation for the seasonal prevalence has as yet been offered. Perhaps it is due to the frequency of "colds" and respiratory affections at this time of the year.

Age Incidence.—Epidemic meningitis, though seen at all ages, is pre-eminently an affection of childhood and adolescence. In the Prussian epidemic of 1905–1907, 6623 of 8198 patients, *i.e.*, 80.12 per cent., were below sixteen years of age. In the Swedish epidemic of 1855–1860 there were, according to Hirsch, 889 cases below fifteen years of age, 328 between sixteen and forty years, and only 50 cases over fifty years, in a total of 1267 fatal cases. Goeppert in Silesia saw 14.46 per cent. of his cases in the first two years of life. On the other hand, in a large number of military epidemics children have escaped entirely. In some of the non-military outbreaks, as at Montgomery, Alabama, adult victims were in the great majority.

The pronounced susceptibility of infants and children to meningococcic infection has received a number of explanations, no one of which is quite satisfactory. Cuneo and Veau claim to have found, during the periods of infancy and childhood, direct anatomical communication in the sphenoid bone between the lymphatics of the nasopharynx and the meninges. These lymphatic canalicules become obliterated in adult life. To attribute the greater incidence of meningitis in childhood to this alleged anatomical condition at the base of the cranium would necessitate the adoption of the view that infection of

the meninges takes place by direct extension from the nasopharynx. As we shall see in a subsequent chapter, there are many weighty reasons that speak against this assumption. Westenhoeffer attributes the predisposition to meningeal infection in childhood to the hyperplastic condition of the adenoid tissue at this period of life. His pathologic studies showing the more frequent occurrence of the "lymphatic state" in those who contract the disease, as contrasted with those who escape infection, are not borne out by the investigations of E. Meyer and others. Moreover, the special susceptibility of childhood is not an exclusive feature of meningococcus meningitis. A number of infectious processes exhibit the same peculiarity. The frank admission must be made that the special factors involved in this phase of infection and immunity are not known.

Sex Incidence.—The influence of sex is not a factor of importance. Epidemics in which the disease attacked a greater number of individuals of one or the other sex are reported in the literature. As a rule, however, the distribution of the disease is about equal in the two sexes.

Race Incidence.—The relative incidence of the disease among the Caucasian and African races in regions inhabited by both has varied greatly in different epidemics. In the early epidemics in New

Orleans and Memphis, negroes were chiefly affected; while, in the recent epidemic in Texas, three times as many whites as negroes contracted the disease.

Influence of Hygienic Conditions.—Epidemics of meningitis are seen most often in the crowded districts of a city or province. In New York and other large cities the densely populated quarters inhabited largely by immigrants have repeatedly borne the brunt of an epidemic. The recent severe outbreaks in Silesia and Westphalia claimed most of their victims among the families of the miners working in the dark and damp coal galleries. Jehle has shown that the infection could be traced to the men working in the mines, and not to the intercourse existing between their families. This he attributes to the great frequency of catarrhal conditions of the pharynx existing among the miners and to their habit of indiscriminate expectoration.

It is probable that the frequency of epidemics among soldiers is due to overcrowding in the barracks. It has been repeatedly observed that newly arrived recruits fell victims to the disease. This predisposition has been attributed to fatigue as a result of the strenuous drills to which the recruits had not previously been accustomed. However, if this were the case we should expect to find an increase of the disease during campaigns. Meningococcus meningitis, however, is not a war pestilence.

The character and condition of the soil, a frequent topic of controversial discussion in other epidemic diseases, elevation, and degree of moisture play a rôle of subordinate importance. Epidemics of meningitis have been equally as frequent in sandy and alluvial soil, and in hilly and level regions.

The Condition of the Patient.—A great number of victims have been in perfect health at the time the disease was contracted. Traumatism to the base of the cranium is mentioned occasionally in the casuistic literature. In the vast majority of the cases this etiologic factor has not been present. In many epidemics of meningitis a simultaneous increase in a number of infectious diseases, such as scarlet fever, influenza and pneumonia, has been noted.

Sporadic Cases.—At the present time it is hardly necessary to insist on the identity of the sporadic and epidemic forms of meningococcus meningitis. A considerable number of isolated cases occur annually in all the larger cities. The approach of an epidemic is frequently heralded by an increase in the number of cases. A similar increase in the sporadic incidence of meningitis is seen in the wake of an epidemic. This is well shown in the statistics of New York City.

1890	136 cases
1891	189 cases
1892	230 cases

1893	469 cases	(epidemic)
1894	214 cases	
1895	204 cases	
1896	173 cases	
1897	221 cases	
1898	310 cases	
1899	372 cases	
1900	201 cases	
1901	201 cases	
1902	190 cases	
1903	195 cases	
1904	1083 cases	(epidemic)
1905	2755 cases	
1906	1032 cases	
1907	828 cases	
1908	380 cases	
1909	346 cases	
1910	342 cases	
1911	266 cases	
1912	250 cases	

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CHAPTER IV

Mode of Dissemination

Having established the contagious nature of meningococcus meningitis, the problem of the mode of its dissemination remains to be discussed. The earlier observers, even those who suspected the infectious nature of the disease, were at a loss how to explain the mode in which the disease was transmitted. Although catarrhal inflammation of the nasopharynx is a condition frequently present in meningococcus meningitis, it rarely gives evidence of its existence by pronounced subjective or objective symptoms. It is the more likely to be overlooked as the patients are often apathetic and stuporous. The coryza sometimes present in meningitis, though much less frequent than the inflammation of the nasopharynx, naturally first engaged the attention of the earlier observers, and nasal cultures were first employed in the search for the meningococcus. A great advance in our knowledge of this phase of the problem was made when the meningococcus was demonstrated in the throat of meningitis patients. Kiefer and Councilman, Mallory and Wright found meningococci in the throat of patients, but it remained for Albrecht and

Ghon, in 1901, to establish the frequency of this phenomenon. Their observations were confirmed by Lord, Weichselbaum, and all observers of the recent epidemics in Germany, America, England, and France. The earlier results were frequently negative. When it was realized what a delicate organism the meningococcus is, cultures were made under better conditions, and positive results became more numerous. At first v. Lingelsheim found the meningococcus in only 182 out of 787 cases, or 23.12 per cent.; when the cultures were incubated at once, 46 out of 49 cases, or 93.8 per cent. yielded positive results. That the meningococcus disappears rapidly from the nasopharynx of meningitis patients is well shown by the statistics of this observer, which are as follows:

Day of disease.	Number of specimens examined.	Number of specimens positive.	Percentage of positive results.
First to fifth day	156	104	66.6
Sixth to tenth day	57	14	24.56
Eleventh to thirtieth day	62	7	11.29
Twenty-first day or later	115	5	4.39

The figures of Goodwin and v. Sholly and Netter and Debré exhibit the same tendency.

	Goodwin and V. Sholly.	Netter and Debré.
	p. ct.	*p. ct.*
First week	12 out of 22 = 54.5	78.55
Second week	5 out of 15 = 33.3	60.0
Third week	.....	50.0
Fourth week	1 out of 16 = 6.25	25.0
After 1 month	.....	15.35

By itself the presence of the meningococcus in the nasopharynx of *patients* fails to explain the spread of the disease, which, as we have seen, rarely occurs directly from patient to patient. The natural history of the meningococcus makes it improbable that the disease is transmissible through the agency of the atmosphere or lifeless objects. Its extreme susceptibility to drying renders its life outside the body a precarious one. The problem of the mode of transmission of the disease received its final solution when it was discovered that the nasopharynx of persons coming in intimate contact with patients harbored the meningococcus. This fact was first discovered by Albrecht and Ghon in 1901. They found the meningococcus in the throat of a man whose child died of meningitis. Since this epoch-making discovery an extensive literature has accumulated tending to show the existence of a large number of healthy germ carriers. It has been estimated by Flügge that the number of carriers is ten to twenty times as great as the number of meningitis cases developing during the same period. The same observer finds that seventy per cent. of the individuals living in close proximity to a meningitis patient become carriers. The results of the most important investigations on this phase of the subject are shown in the following table, taken from Frost:

Demonstration of the Meningococcus in the Nasopharynx of Apparently Healthy Persons.

Locality.	Condition.	Percentage of persons examined shown to be carriers.
Dieudonné (1906), during small outbreak in garrison at Munich, examined (Centralblatt f. Bakt., 1906, p. 418):	(*a*) 39 men from a dormitory in which there had been several cases of meningitis—found 5 carriers.	12.8
	(*b*) 29 soldiers from the same battalion who applied for treatment on account of nasopharyngeal troubles—found 4 carriers.	13.8
	(*c*) 20 men from a regiment in which there had been no case of meningitis—found no carriers.	0.0
Osterman (1905–06), during an epidemic in vicinity of Breslay, examined (Deutsch. med. Wochenschr., 1906, 1, p. 414):	(*a*) 24 persons, members of families in which there were cases of meningitis—found 17 carriers.	70.8
	(*b*) 51 school children in a town where there had been a recent case—found 2 carriers, associates of patient's sister.	4.0
	(*c*) 10 persons not in contact with any case—found no carriers.	0.0
Bochalli, in garrison at Beuthen, Prussia, in which there had been a case recently, examined (Zeitschr. f. Hyg. u. Infektionskrank., Bd. lxi, pp. 454–464):	(*a*) 16 men associated in dormitory with a recent patient—found 10 carriers.	62.5
	(*b*) 114 men of the same company, not roommates of patient—found 13 carriers.	11.4
	(*c*) 355 men in the 3 other companies of same garrison—found 19 carriers.	5.4
	(*d*) Control; 40 men from 2 battalions in Gleiwitz, where there had been no cases of meningitis—found no carriers.	0.0
Von Lingelsheim, in vicinity of Beuthen, Prussia, during an epidemic, examined (Zeitschr. f. Hyg. u. Infektionskrank., 1908, Bd. 59, pp. 457–483):	(*a*) 387 persons in close contact with cases of meningitis—found 28 carriers.	7.23
	(*b*) 127 persons not in contact with cases—found no carriers.	0.0
	(*c*) 184 children suffering from scarlet fever, measles, whooping-cough (apparently unassociated with any cases of meningitis—found no carriers.	0.0
Bruns and Hohn, in valley of the Ruhr, Prussia, during severe epidemic in 1907, examined (Klin. Jahrbuch, Jena, 1908, Bd. xviii, pp. 285–310):	(*a*) 3154 healthy persons in community where epidemic prevailed—found 465 carriers.	14.7
	(*b*) Of the above specimens were taken in the immediate vicinity, under the investigators' supervision, in 1786 cases—showing 401 carriers.	22.5
	(*c*) Including only members of families in which cases of meningitis had occurred—609 were examined and 224 were found carriers.	36.78
	(*d*) Persons in the community examined under favorable circumstances during and after the epidemic, not directly associated with any cases of meningitis; 380 examined—30 found carriers.	7.9
Herford, during epidemic at Altona, examined (cited by Netter and Debré, loc. cit., p. 44):	172 persons in the families with cases of meningitis—found 43 carriers.	25.0

Demonstration of the Meningococcus in the Nasopharynx of Apparently Healthy Persons—Continued.

Locality.	Condition.	Percentage of persons examined shown to be carriers.
Trautmann, at Hamburg, examined (cited by Netter and Debré, loc. cit.):	261 persons in families with cases of meningitis—found 24 carriers.	9.2
Mayer, Waldmann, Fürst, and Gruber, examined (Muench. med. Wochenschr., 1910, vol. 57, p. 1584):	(*a*) 1911 men from various garrisons from 1908 to 1910 at the time of occurrence of cases of meningitis in the respective garrisons—found 47 carriers (associated with a total of 46 cases of meningitis).	2.46
	(*b*) in 1910, at Munich, examined the whole garrison, 9111 men. It is implied that there was no recent case of meningitis in the garrison at this time, but there had been one or more cases annually since 1908 in each of the barracks mentioned—158 of these men were found to be meningococcus carriers.	1.73
Kolle and Wassermann, in Berlin, in 1906 (cited by V. Lingelsheim), examined:	114 residents of Berlin; found 2 carriers, both of whom had been associated with suspicious cases of meningitis—possibly sporadic cerebrospinal meningitis.	1.8
Droba and Kucera, 1906, examined (cited by von Lingelsheim).	160 children in a community free from meningitis—found no carriers.	0.0
Kutscher, 1905 (cited by Kelsch, Rev. d'Hygiene, 1911, vol. 33, pp. 1–53), examined.	56 patients in Berlin for various affections—found 4 carriers.	7.4
Huber and Kutscher (cited by Kelsch, Rev. d'Hygiene, 1911, vol. 33, pp. 1–53), examined.	A detachment of 408 soldiers free from meningitis both before and after the time of examination—found 8 carriers.	2.0

That the number of healthy carriers, both in the immediate vicinity of the patient and in the general community, runs parallel with the number of persons affected by the disease is shown in the composite table on page 60 from Bruns and Hohn.

Similar results are reported by Netter and Debré, who found 41.66 per cent. carriers in the months of

March, April, and May, as contrasted with 26.66 per cent. during June, July, and August.

	No. of cases of meningitis.	No. of well persons examined.	No. of carriers found.	Percentage of carriers among well persons examined.	No. of families examined.	No. of families with carriers.	Total no. of persons in these families.	No. of carriers among these persons.	Percentage of carriers among these persons.
March....	148	56	34	60.7	7	7	23	14	61.7
April.....	278	360	116	32.2	39	37	135	67	50.0
May.....	327	408	97	23.8	43	40	172	81	47.0
June.....	188	352	84	23.9	23	18	93	34	36.6
July.....	146	323	49	15.1	21	11	67	18	27.0
August ...	68	287	21	7.3	22	7	119	10	8.5

A point of great importance in the successful demonstration of the meningococcus in the nasopharynx is the rapidity with which cultures are incubated and studied. On this point the studies of Bruns and Hohn are very instructive:

Of 593 specimens taken by them personally or in their presence and incubated immediately, 192 were positive, or 32.4 per cent.

Of 1193 specimens sent to them by special messenger, 209 were positive, or 17.5 per cent.

Of 1324 specimens sent by mail within 24 hours, 63 were positive, or 4.7 per cent.

Of 30 specimens sent by mail within 48 hours, none were positive, or 0.0 per cent.

The relative distribution of carriers among the members of a family was found by Bruns and Hohn to be as follows:

Of 113 fathers examined 60 were carriers, or 53.09 per cent.

Of 114 mothers examined, 39 were carriers, or 34.21 per cent.

Of 360 brothers or sisters examined, 118 were carriers, or 32.77 per cent.

Of 22 other members examined, 7 were carriers, or 32.81 per cent.

The number of carriers not only varies with the period of the epidemic and the season of the year, but with the intimacy existing between the patient and his neighbors. Bochalli found 10 carriers among 16 soldiers occupying the same barrack with a patient,—62.5 per cent.; 114 soldiers belonging to the same company yielded only 13 carriers, or 11.4 per cent.; 19 carriers were found among 355 soldiers of the same battalion, or 5.4 per cent. Moreover, the hygienic surroundings play a determining rôle on the number of carriers. It has been seen that epidemics of meningitis occur most frequently in overcrowded quarters. It is but natural to suppose that this is due to the greater number of carriers. Such indeed has been found to be the case. In poor families Netter and Debré encountered 31.39 per cent. carriers, while among those in comfortable circumstances only 15.38 per cent. carriers were found. In the mining districts, where the miners work in close proximity to each other, the percentage of carriers is very large. On

the other hand, in hospitals the number of carriers among patients, physicians, and nurses is almost *nil.* At the New York Hospital, in which at times there are six or seven meningitis cases, repeated examinations by Elser and Huntoon failed to reveal the presence of carriers among patients, physicians, or nurses. To this is attributable the well-known fact that instances of hospital contagion are so rare.

That the intensity of an epidemic runs parallel with the number of carriers is shown by the comparative statistics in Silesia, Paris, and Hamburg (Netter and Debré). In the very severe epidemic of Silesia in 1904–1905, with its thousands of victims, there were about 327 carriers in the immediate vicinity of each patient. The moderate Parisian epidemic of 1908–1909 gave only 22.7 per cent. carriers. In the comparatively mild epidemic at Hamburg during 1907, in which only 93 persons contracted the disease, only 9.6 per cent. were found to be carriers.

Persistence of the Meningococcus in the Nasopharynx of Healthy Persons.—Mayer, Waldmann, Fürst, and Gruber classify carriers according to the persistence of meningococci, as follows:

Periodic, showing alternate appearance and disappearance of the meningococci.

Persistent, in whom meningococci are constantly present for weeks or months.

Temporary, in whom meningococci are present only for a short period.

Of 96 carriers examined:

Six belonged to the periodic class, or 6.25 per cent.

Twelve belonged to the persistent class, or 12.50 per cent.

Seventy-eight belonged to the temporary class, or 81.25 per cent.

As a rule, the meningococci disappear from the nasopharynx of healthy persons within three weeks. Selter, however, obtained positive cultures after 4 and 7 months.

Presence of Carriers among Individuals not Exposed to Infection.—The vast majority of researches dealing with this phase of the subject have yielded negative results.

Kolle and Wassermann (112 individuals), v. Lingelsheim (125 individuals), Kutscher (52 individuals), and Goodwin and Sholly (55 first-year medical students) failed to find carriers in individuals during a time when no epidemic prevailed or in those not exposed to infection. The results of Mayer, Waldmann, Fürst, and Gruber, who found 158 carriers among the whole garrison at Munich, consisting of 9111 men,—*i.e.*, 1.73 per cent.,—are unique, and perhaps attributable to the occurrence annually of one or more cases in each barrack. Considering the

uniformly negative results of other observers, their contention that the meningococcus, like the pneumococcus, is almost ubiquitous in the respiratory tract of man, is hardly justifiable.

Distribution of the Meningococcus in the Respiratory Tract.—In the earlier investigations the search for the meningococcus was restricted almost wholly to the nasal mucus. The results were often meagre. The bacteriologic studies of v. Lingelsheim at Beuthen, as well as the post-mortem results obtained by Westenhoeffer, who found early catarrhal inflammation of the nasopharynx in all his cases of meningitis, soon led to an important change in the method of investigation. Cultures were no longer taken from the nose, but from the nasopharynx by the oral route, with much more satisfactory results. While the meningococcus may be found in the tonsils, in the anterior and posterior nasal fossæ, and even in the saliva, its site of election in most cases is the upper part of the nasopharynx and the part of the posterior nares in its immediate vicinity.

The Local and General Condition of Health of the So-called "Healthy" Carriers.—Most of the carriers present no subjective or objective symptoms, and are in fact in perfect health. Not so rarely, however, posterior rhinoscopy reveals the presence in the upper part of the nasopharynx of an inflamed and

reddened mucous membrane covered with a viscid mucopurulent secretion. Still more rarely the meningococcus betrays its presence by a severe coryza, which may last 2 to 3 days or several weeks. Even in the presence of an inflammation of the nasopharynx there is almost never any complaint of local pain or difficulty in swallowing. In exceptional cases there may be slight transitory febrile movement, associated with slight malaise, and mild headache. These cases are perhaps the connecting links between perfectly healthy carriers and abortive forms of meningitis or meningococcic sepsis without involvement of the meninges.

Source of the Meningococcus found in the Nasopharynx of Meningitis Patients.—It is conceivable that the meningococcus may come from one of two sources,—namely, from the external world by inhalation of contaminated air or from the infected meninges by way of the lymphatics at the base of the brain. For the first source nearly all the data previously adduced speak, such as the early appearance and rapid disappearance of the meningococci, the presence of meningococci before the onset of meningeal symptoms, and the analogy with healthy germ carriers where the atmospheric source is the only possible one. That some of the meningococci may come from the meninges by way of the lymph-channels is suggested

by the finding of Gram-negative cocci in the nasopharynx of monkeys suffering from experimental meningitis. Unfortunately, Flexner, who made these observations, did not identify the organisms in cultures. The occasional reappearance of meningococci in the throat of patients during an exacerbation at a late stage of the disease, as observed by Elser and Huntoon, would also speak for this assumption. In experimental poliomyelitis, the passage of the virus from the brain to the mucous membrane of the upper respiratory tract has been repeatedly proved.

Mode of Contagion.—The data drawn from epidemiologic and bacteriologic studies justify the conclusion that the usual mode of transmission of the disease is directly from one individual to another. This does not necessarily mean that transmission is from patient to patient. Indeed there is reason to believe that in most cases the source of contagion is a healthy or apparently healthy meningococcus carrier. As we have seen, it has been estimated that there are ten to twenty times as many carriers as there are patients. Moreover, individuals suffering from meningitis are confined to bed, thus limiting the number of persons with whom they come in contact. The somnolent or apathetic condition of many of the patients also lessens the danger of transmission of the

disease by expectoration of germ-laden sputum. In the cases of patients in the period of childhood there is still less likelihood of the disease being transmitted, as most of these swallow their sputum. The strange fact that cases of hospital contagion are so rare is probably due to the greater number of meningitis patients in these institutions being children. In the few instances where the source of contagion could be traced to inmates suffering from meningitis, the patients were adults. The question has been raised whether the meningococci found in the throat of healthy germ carriers are not attenuated or avirulent forms of the organisms. By experimental studies it is rather difficult to determine the answer to this question. We have seen how feeble and inconstant is the pathogenicity of this organism for the ordinary laboratory animal. However, the occurrence of meningitis in persons subsequent to their having been proved to be carriers, as reported by Stuhlen, Bruns and Hohn, and Bochalli, shows that at least in these cases the organism was virulent to the extent of being capable of producing an infection of the meninges.

It is probable that transmission of the disease occurs most frequently through the medium of minute particles of moisture (droplets of Flügge) derived from the respiratory tract of an individual harboring the meningococcus. It is possible that conveyance

of infection may also occur by hand-shaking, kissing, the use of common eating or drinking utensils, same handkerchiefs or towels, or food contaminated by soiled fingers. For the preservation of the pathogenic power of the infective material it is necessary that the time elapsing between its elimination and reception should be short. Indirect contagion through the agency of inanimate objects, though possible, is not likely. The low degree of viability of the meningococcus outside of the human body speaks against this assumption. At any rate, such a mode of transmission of the disease has thus far not been proved.

The great number of meningococcus carriers during the epidemic incidence of meningitis show the great receptivity of the human body for the meningococcus at such a period. There is, however, a marked difference between receptivity and susceptibility to meningeal infection. Most of those individuals that become meningococcus carriers escape infection. It is only a comparatively small number who, as a result of local or general susceptibility, succumb to infection. The nature of the barriers that prevent the passage of the meningococcus beyond the boundaries of the mucous membrane of the respiratory tract is not known. We merely know that in children and individuals living under unhygienic conditions they

offer less resistance to the invasion of the meningococcus.

The high degree of receptivity and low degree of susceptibility to meningeal infection exhibited by the human body toward the meningococcus explain some of the bizarre features encountered in the study of the epidemiology of the disease, such as the propagation by leaps and bounds and the simultaneous outbreak in localities far removed from one another.

Causes of Epidemic Outbreaks.—Theoretically there are only two possible factors that can enter, alone or in combination, in the causation of an epidemic,—namely:

Sudden increase in virulence of the specific organism.

Sudden general increase in susceptibility to infection by the specific organism.

The possibility of a rapid enhancement of diffusibility of the organism should be borne in mind. Even if such a phenomenon were demonstrable in every epidemic, it could on further analysis be shown to be dependent upon one or the other of the two factors named above. Rapid diffusibility, however, can not possibly explain the simultaneous appearance of epidemics in parts thousands of miles distant from one another. Yet such outbreaks have been repeatedly

observed from the very earliest history of meningococcus meningitis.

Experimental work, with the exception of that of Ruppel which remains unconfirmed, has failed to produce an increase in the virulence of the meningococcus by any method known to bacteriology. Nor has it been shown that strains of the meningococcus cultivated from patients during an epidemic are regularly more virulent than those derived from sporadic cases.

The existence of a general decrease in human resistance to meningococcic infection is still less susceptible of scientific proof, as experimental demonstration is out of the question. The increased incidence of other contagious diseases during outbreaks of epidemic meningitis should lead us to assume the temporary appearance of a common factor. It is less difficult to conceive of a general decrease in resistance to infections than of a sudden and simultaneous increase in virulence of a number of organisms.

In pandemic outbreaks a cosmic factor—such as change in climatic conditions—must necessarily be present, but at present it is entirely a matter of conjecture whether its action is directly in increasing the virulence of the meningococcus or the susceptibility of the human body.

Mode of Invasion of the Meninges by the Menin-

gococcus.—While practical unanimity has been reached regarding the usual portal of entry of the organisms in the body, opinions are still divided on the question of the mode of invasion of the meninges. The proximity of the roof of the nasopharynx to the base of the brain naturally suggests the likelihood of direct penetration of the meningococcus along the structures in this region. Support was lent to this assumption by the early pathologic studies. Westenhoeffer found constant redness, swelling, and hypersecretion of the mucous membrane of the nasopharynx and practically constant involvement of the sphenoidal sinuses. This observer, in common with others, found the first traces of exudate in the region of the optic chiasm and hypophysis,—*i.e.,* structures contiguous to the sphenoidal sinuses. But a more careful study of his material soon led Westenhoeffer to abandon his earlier view,—that the meningococcus gains access to the meninges by direct extension. The perihypophyseal inflammation was confined to the superior and lateral surfaces, which would not be the case if the invasion occurred by direct extension along the sphenoid bone. Moreover, sections through this bone failed to reveal either the presence of the meningococcus or evidence of inflammatory changes in the deeper portions. Similarly there is no histological evidence of the spread of the inflammatory process

along the cranial and spinal nerves and the lymphatics around the carotid.

There being no anatomical proof for the sphenoidal route, two other modes of direct invasion remain to be considered,—namely, the trans-ethmoidal and the aural route. Cuneo and André claim to have found in the cribriform plate of the ethmoid a system of anastomosing canalicules which in the infant communicate directly with the subarachnoid space at the base of the brain. It has been proved that the circulation of lymph in this region is from the base of the brain outward toward the nasopharynx. It has been assumed by a number of observers that the meningococcus traverses this region in the opposite direction. But in the human infection at least, neither Mackenzie and Martin nor Netter and Debré have succeeded in demonstrating the meningococcus in any part of the ethmoid bone. In experimental meningitis, Gram-negative diplococci were found by Flexner in this region. But, as infection occurred by intradural infection, the organisms were evidently in the process of being excreted. There is consequently no direct proof of the trans-ethmoidal invasion of the meningococcus.

That the infection extends along the Eustachian tubes and middle and internal ears is unlikely, by reason of the fact that in most of the cases there is no

evidence of early inflammation of the middle ear. The validity of the argument in favor of direct extension from the nasopharynx, by reason of the alleged appearance of the exudate first at the base of the brain, loses its whole force when we consider that a similar localization takes place in tuberculous meningitis, in which the infecting organism undoubtedly reaches the meninges by the blood stream. Similarly in experimental meningitis, produced by intradural infection of the meningococcus, the primary site of the exudate is also found at the base of the brain. Moreover, Busse has demonstrated that the exudate appears simultaneously at the base of the brain and in the spinal meninges.

The recent successful cultivation of the virus of poliomyelitis in the form of a microscopically visible organism brings poliomyelitis and meningitis into closer relationship. In both the specific causative agent has a special affinity for the tissues of the central nervous system. Moreover, in both diseases the mucous membrane of the nasopharynx seems to be, in the vast majority of the cases, the primary portal of entry. So that the facts established regarding the mode of invasion of the central nervous system by the virus of poliomyelitis should have some bearing on the problem of the meningococcus invasion of the meninges. Flexner has shown that when a monkey is

killed forty-eight hours after an intranasal inoculation of the virus, and the brain, spinal cord, and olfactory lobes separately inoculated into other monkeys, infection is produced by the olfactory lobes only. This proves that the virus had not in this brief period reached the more distant parts of the central nervous system, and that the infection is an ascending one along the olfactory filaments. Unfortunately, in the case of meningitis no one has as yet succeeded in producing the disease in animals by intranasal inoculation. Were this possible, the question of the mode of invasion would probably receive its immediate solution. In brief, at the present time there are no direct facts in support of the assumption that the meninges are invaded by direct ascension of meningococcus from the nasopharynx.

On the other hand, a number of facts speak for the primary invasion of the blood and secondary infection of the meninges. Blood cultures have been positive in about one-third of the cases examined, and it is probable that with improvement in technic positive results will become more frequent. However, only the results obtained in the earliest period of the disease have any bearing on this question. Salomon, Martini and Rohde, Marcovitz, and Andrewes have demonstrated the meningococcus in the blood previous to the appearance of pronounced meningeal

symptoms. At autopsy, lesions in the heart and other viscera have been found in individuals that died within twenty-four hours of the onset of the disease. Not infrequently characteristic eye symptoms have been found that were in the same stage as those of the central nervous system. On the other hand, it must be admitted that in most of these cases the clinical course was dominated by the septic process, and differed considerably from that of the ordinary type of meningococcus meningitis. Moreover, in the majority of the cases, but few organisms could be isolated, indicating a transient invasion of the blood stream.

Elser and Huntoon consider the sudden onset an argument in favor of the primary invasion of the blood. In otogenic and traumatic meningitis, in which local infection of the meninges is likely, the symptoms develop more gradually and irregularly.

Solution of this difficult problem is apparently only to be attained by animal experimentation. Unfortunately, so far all attempts to produce a characteristic meningitis in animals by intranasal, intrapharyngeal, or intravenous inoculation of the meningococcus have resulted in complete failure. The intradural production of meningitis, which has succeeded in the hands of v. Lingelsheim and Leuchs, Flexner, Stuart McDonald, and others, does not aid

us in the solution of this question. By injecting intravenously an organism closely resembling the streptococcus mucosus, Elser, Huntoon, and Strauss succeeded in producing a meningitis in rabbits, which in its sudden onset after a latent period of several days resembled closely the disease in man. The present state of our knowledge permits us to state that there is some evidence, but no conclusive proof, that the meningococcus primarily invades the blood and secondarily the meninges.

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CHAPTER V

Pathologic Anatomy

Before proceeding with the description of the pathologic anatomy of this disease, it seems desirable to recall some features of the anatomy of the meninges and central nervous system which are important in this connection. While some anatomists describe two membranes, the pia-arachnoid and dura, it seems best for our purpose to divide the meninges into three,—namely, pia mater, arachnoid, and dura (Fig. 8). The pia is a delicate membrane composed chiefly of blood-vessels which penetrate the substance of the central nervous system at innumerable points. It forms the visceral layer of the leptomeninges, and follows closely the irregularities of the surface of the brain and cord, dipping into the sulci and projecting into the ventricles in the form of a network of capillaries which are known as the choroid plexuses. These capillaries are lined by a layer of epithelium, which probably plays an important part in the secretion of cerebrospinal fluid. The arachnoid is the outer of the two leptomeninges. It follows more closely the reflections of the inner layer of the dura and is in part only loosely connected with the pia mater by means of delicate septa.

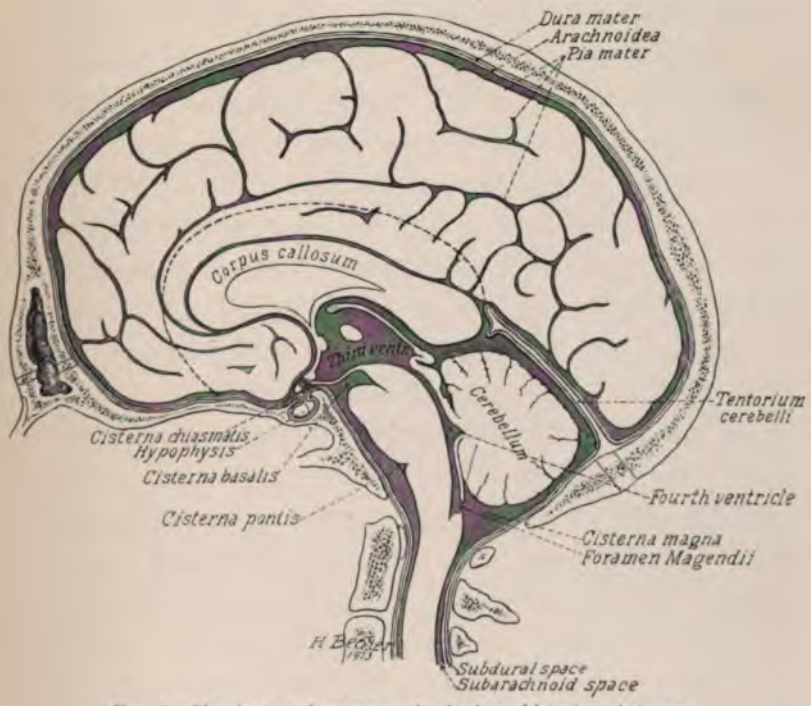


FIG. 8.—Showing membranes covering brain and location of cisterna.

It does not dip into the sulci. At the base and lateral aspect of the brain there is distinct separation between the pia and arachnoid, leaving a number of quite large spaces which bear the name of cisterna. The most important of these are the cisterna chiasmatis, basalis, pontis, and cerebello-medullaris or cisterna magna. They form intercommunicating portions of the subarachnoid space at the base of the brain. The cisterna magna communicates freely with the fourth ventricle through the mediation of the median foramen of Magendie and the lateral foramina of Key and Retzius or Luschka. It drains into the subarachnoid space of the spinal canal.

The spinal arachnoid lines the inner surface of the dura throughout its whole extent, while the pia closely invests the spinal cord, thus leaving a considerable space between the two membranes. Through this space pass many slender bands and trabeculæ which connect the pia with the arachnoid. In the vicinity of the pia these trabeculæ greatly increase in number. In this region there is found a delicate fenestrated membrane running the whole length of the cord, which partly shuts off the space along its inner surface, known as the epi-pial space, from the general subarachnoid space. This accounts for the fact that occasionally a comparatively clear fluid is obtained on lumbar puncture in cases where a subsequent

autopsy shows the cord enmeshed in a thick exudate. The subarachnoid space is further subdivided into an anterior and a posterior half by the ligamentum denticulatum.

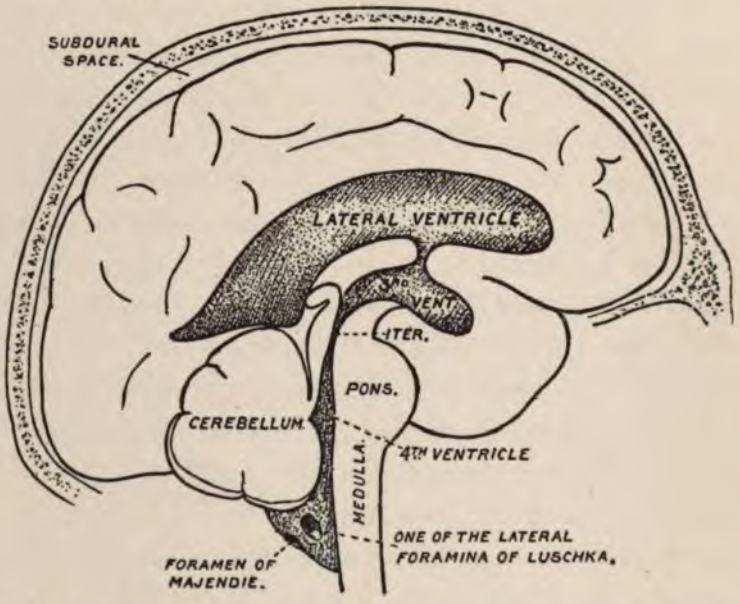


Fig. 9.—Showing ventricular system of brain and foramina of 4th ventricle. (Still.)

The ventricular system (Fig. 9) of the brain consists of the lateral ventricle in each cerebral hemisphere; the third ventricle, situated between the two hemispheres and connected with the former by means of the foramina of Monro; and the fourth ventricle, lying between the cerebellum, pons, and medulla, and communicating with the third ventricle by means

PLATE I

Macroscopic lesions of convexity of brain meningococcus meningitis. (Koplik.

PLATE II

Side view of brain meningococcus meningitis. (Koplik.)

of a narrow channel, the aqueduct of Sylvius. The fourth ventricle is directly continuous with the central canal of the cord.

Macroscopic Appearance of the Meninges and Central Nervous System in the Acute Stage (Plates I and II.)—The macroscopic lesions of the central nervous system in this disease are not characteristic. They differ but little from the changes seen in other forms of acute suppurative meningitis. The dura is tense and at times its vessels show considerable injection. Its inner surface is shining, and small hemorrhages may be present in those portions which cover the base of the brain. On opening the dura, a considerable amount of turbid fluid or pus may escape from the subarachnoid space. The picture presented varies greatly with the acuteness and severity of the infectious process. In some cases a purulent exudate forms within twenty-four hours from the onset of the disease; in others pus is not found in the first few days.

In fulminating cases there is intense injection of the blood-vessels of the leptomeninges, at times giving a pinkish hue to the entire surface of the brain. The brain seems to be increased in volume, as evidenced by flattening of the gyri. The normal transparency and shimmer of the meninges are lost. In the sulci a small quantity of turbid fluid is usually seen on the

convexity of the brain. At the base, especially in the vicinity of the hypophysis, there is often present a small collection of pus.

In cases of less severity, where death has taken place in from five to ten days, the exudate is more abundant. It is yellowish-green, thick, and gelatinous. It is most abundant at the base and in the sulci of the convexity of the brain, where it is seen as more or less isolated bands and plaques along each side of a congested blood-vessel. In more advanced cases there is present at times a cap of pus of considerable thickness covering the upper and lateral surface of the frontal lobe and the anterior half of the parietal lobes. This peculiar localization of the exudate is attributed by Goeppert to the distribution of the anterior and middle cerebral arteries. The greater abundance of the exudate at the base is due not so much to the effect of gravity, but to the fact that in this region the subarachnoid space is more voluminous and the membranes have larger meshes. At the base the exudate accumulates first in the region of the optic chiasm, hypophysis, and tuber cinereum. From here it spreads anteriorly along the optic nerves, laterally over the lateral aspects of the frontal and parietal lobes, and posteriorly over the inferior surfaces of the pons, medulla and cerebellum, and the cisterna magna. Having reached this region, the

exudate flows along the cerebral peduncles and the furrow between the parietal lobe, pons, and cerebellum, and then covers the superior vermiform process and upper surfaces of the lobes of the cerebellum.

On exposure of the membranes of the cord, the dura is found distended. Its vessels are markedly injected, and the fat lobules usually found along its outer surface often show small hemorrhagic extravasations and occasionally purulent infiltration. There is marked congestion of the vessels on the inner surface of the dura. At times there are seen small ecchymoses and fibrinous plaques. The exudate, which is confined almost wholly to the posterior aspect of the leptomeninges, usually appears about the same time as in the meninges of the brain. It is most abundant in the cervical, lower dorsal, and lumbar regions. The parts of the meninges free from exudate show a loss of the normal lustre and transparency. There is visible injection of the blood-vessels of the anterior surface of the meninges. Rarely is a purulent exudate present in this region.

The ventricles in the first days of the disease show little change. Soon thereafter they become somewhat dilated, and are filled with a turbid fluid containing fibrinous flocculi. The ependymal lining becomes lustreless. The choroid plexus is at first

hyperæmic, later it assumes a dull grayish appearance.

The parenchyma of the brain and cord shows few lesions which are apparent to the naked eye. The inflammation is sharply limited to the meninges which are readily stripped off from the brain tissue. The vessels of the gray and white substance are injected, and the cortex seems to be œdematous. Punctiform hemorrhages have been seen more frequently by some observers than by others. Distinct areas of softening are rare, while abscess formation is still more rare. Hemorrhagic foci are less often seen in the cord than in the brain.

Chronic Stage.—The exudate at the convexity usually disappears within fifteen to thirty days. It is replaced by local or general thickening of the meninges. Yellowish-white, dense, and opaque bands are usually seen along the vessels at the convexity. At the base dense adhesions are still more often seen. False cysts may be formed containing clear, turbid, or purulent fluid, producing so-called sacculated meningitis. In stripping off the membranes small portions of the cortex are often torn away. In places the leptomeninges may become adherent to the dura.

The meninges of the cord show similar thickenings, but, as a rule, they are less general and marked than in the meninges of the brain. They are almost

always confined to the posterior aspects of the cord. The spinal-nerve roots may be embedded in a network of false membrane. After convalescence has become established the adhesions are for the most part absorbed. Autopsy at this period may reveal an isolated opaque plaque here and there.

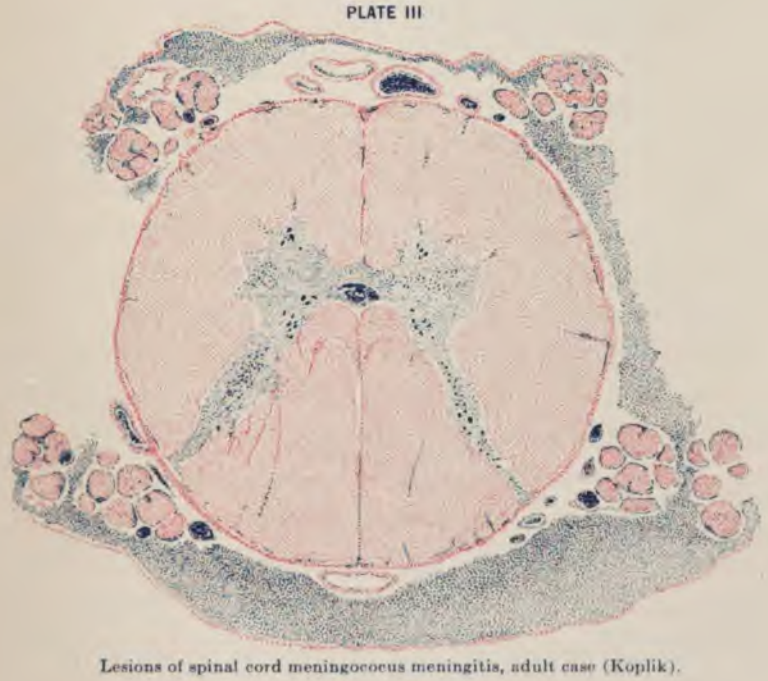
The ventricles in the chronic stage are usually markedly dilated. The ependyma is thickened and irregular. Its lining membrane has partly disappeared. It is covered with granulations which are adherent to the underlying brain tissue. The subependymal tissue is more reticular and œdematous. Pus is often present in the more dependent portions of the posterior and inferior cornua, at a time when it has completely disappeared from the surface of the brain. False membrane may at times obliterate the communications between the various ventricles. The studies of Goeppert show that complete obliteration is not as frequent as it is usually thought to be. In most of the cases studied by him, he demonstrated a free flow of injected fluid from the ventricles into the spinal subarachnoid space.

The parenchyma of the brain and cord shows practically no changes that are apparent to the naked eye.

Microscopic Lesions. Acute Stage.—The essential morbid process is a purulent infiltration of the

leptomeninges. The question of the primary seat of the meningeal inflammation is still an open one. Westenhoeffer contends that the inflammation is primarily localized in the arachnoid, that the disease is a suppurative arachnitis. He bases this assumption chiefly on the fact that in the depths of the sulci where the pia alone is present, the inflammatory changes are less marked than in the more superficial portions. The earliest lesions are seen in the vicinity of the blood-vessels which are markedly dilated. In the walls and within the lumina of the smaller veins are present many leucocytes. At times there is evidence of thrombophlebitis. Gradually the leucocytic infiltration of the meninges becomes more general, the fine trabeculæ and septa of the arachnoid disappear, and larger and smaller spaces are formed containing masses of inflammatory cells. Between the cells there is present a fine granular material representing the coagulated serum of the exudate. There is little fibrin in the early stages of the disease. In the exudate the cell masses are larger and more abundant. The exudate chiefly contains four kinds of cells. The predominant cells are polymorphonuclears, either normal in appearance or degenerated. The lymphocytes are less abundant. In addition to these there are present large cells from two to eight times the size of a polymorphonuclear cell, having a faintly stained,

PLATE III



Lesions of spinal cord meningococcus meningitis, adult case (Koplik).

finely granular protoplasm, and a large eccentric vesicular nucleus. They often contain a number of ingested cells lying in vacuoles of the protoplasm. Their number varies considerably. They were first described in 1865 by Boehmer, who considered them to be the mother cells of the pus-cells which were seen in them. Councilman, Mallory and Wright have been able to follow the various steps of their formation from the connective-tissue cells of the meninges. They may also arise from the adventitia of the blood-vessels. They have been demonstrated in other forms of meningitis. Red blood-cells are present in variable quantities. As a rule they are seen in great numbers. Eosinophiles are almost never present.

The changes in the meninges of the cord (Plate III) are similar to those of the meninges of the brain. The large cells, described above, are not so abundant in the exudate. It is a fact of great significance that the inflammatory process begins simultaneously in the meninges of the brain and cord. Westenhoeffer found the earliest evidence of inflammation in the region of the hypophysis. But, as Busse points out, he failed to make a careful microscopic examination of the cord. The microscope often shows a purulent infiltration in areas of the meninges which to the naked eye appear perfectly normal. As we shall see later, the simultaneous appearance of the inflamma-

tion in the brain and cord speaks strongly for a blood invasion of the meningococcus.

The ventricle and neighboring brain tissue show microscopic changes in all cases. The ependymal lining may be lost in parts and the villi of the choroid plexus may show some desquamation. The sup-ependymal tissue is reticular and œdematous. The blood-vessels in the walls of the ventricles are dilated and surrounded by isolated or grouped leucocytes. These cells tend to accumulate about that part of the periphery of a vessel which is nearest to the cavity of the ventricle. The villi of the choroid plexus are congested and infiltrated with leucocytes.

The cortex of the brain is reticular and œdematous. These changes are particularly marked in the cerebellum. Isolated leucocytes are present in the tissue above the ganglion-cells. At times they are also seen in the white substance of the brain. The blood-vessels of the cortex are dilated. Evidence of some perivascular leucocytic infiltration is present in many cases. It is nevertheless true that the inflammatory process is largely confined to the meninges and that there is but little extension to the parenchyma of the brain and cord. Councilman, Mallory and Wright describe proliferation of the neuroglia and connective-tissue cells in the cortex above the ganglion-cells, beneath the ventricles, and particularly in

the vicinity of foci of hemorrhage and cellular infiltration.

Chronic Stages.—With advance of the inflammation the greater number of the cells in the exudate undergo degeneration and fatty metamorphosis. The nuclei lose their staining power and are later converted into granular detritus. The large cells disappear. Lymphoid and plasma cells appear in greater numbers. Organization of the exudate proceeds by the formation of new connective-tissue cells and capillaries. The yellow opaque areas seen by the naked eye are composed of cicatricial tissue containing few blood-vessels and cells. In the ventricles the organized exudate is often seen to be connected with the tissue beneath the ependyma. The walls of the ventricles show a considerable number of perivascular nodes which may project into the cavity of the ventricle. They are largely composed of lymphoid cells. Suppuration of the nodes is extremely rare. Busse has observed along the outer border of the cortex of the cerebellum a continuous layer of cells whose nuclei are placed at right angles to the circumference of the cerebellum (palisade cells). These are normally seen in fetal life and early infancy. Their presence in the chronic stages of meningitis is interpreted by him as a reversal to fetal structure.

In subacute and chronic cases the pyramidal cells and especially the cells of Purkinje in the cerebellum show evidence of degeneration in the form of vacuolization and chromatolysis.

In the cord Liebermeister and Lebsanft have demonstrated destruction of the myelin sheaths and degeneration of the fibres in the peripheral zones. This process was especially marked in the more protracted cases. The ganglion-cells of the anterior horns give evidence of degeneration. Degeneration of the posterior nerve-roots occurs in the protracted cases as a result of the purulent infiltration of the arachnoid which ensheaths the roots. The cells of the spinal ganglia may show similar degeneration.

The degeneration of the nerve tissue proper is due to imbibition of toxin. Similar changes result from the action of other micro-organisms which have no selective affinity for the nervous system. The alterations, as a rule, are not permanent.

The cranial nerves are involved as a result of the extension of the inflammation along the arachnoid which envelops them. The 2d, 3d, 4th, 5th, 6th, 7th, and 8th are most often affected. The Gasserian ganglion is often found embedded in pus at an early stage of the disease. The purulent exudate may extend along its three branches to the orbit, otic gang-

lion, and sphenopalatine ganglion. The substance of the ganglion does not undergo suppuration. In protracted cases the peripheral nerves may show degenerative changes.

The Meningococcus in the Nervous System.—The demonstration of the meningococcus in the acute stages is not difficult, providing the examination is not delayed. In the exudate the meningococcus is often found in great numbers, both within and without the cells. In the meninges, especially of the cord, it is less abundant. This may in part be due to the process of hardening of the tissues which may exert an injurious action on the staining properties of the meningococcus. In the chronic cases the organism is found with great difficulty. It has been demonstrated in areas of focal softening of the brain and cord.

The Meningococcus in the Blood.—The meningococcus was first found in the blood by Gwyn in a patient of Osler. It has also been found by Cochez and Lemaire, Jakobitz, Martini and Rohde, Lenhartz, Marcovitz, Robinson, Dieudonné, Duval, and others. Elser demonstrated the meningococcus in 11 out of 41 cases. In a number of cases it has been found in patients free from meningitis (Salomon, Liebermeister, Andrewes and Bovaird).

LESIONS IN OTHER PARTS OF THE BODY

Upper Respiratory Tract.—The lesions of this tract have been studied with minute care by Westenhoeffer. He found marked hyperæmia, slight œdema, and increased secretion of the adenoid tissue of the nasopharynx in the early stages of the disease, due to infiltration of lymphoid and plasma cells. The nasal mucous membrane shows similar but less marked changes in adults. In children inflammation of the nose occurs at a later stage as a complication. The tonsils are much less often affected. The mucous membrane of the sphenoidal sinus and the antrum of Highmore are somewhat hyperæmic. The ethmoidal cells show still less change. The meningococcus has never been found either in the bones or sinuses of this region.

Lower Respiratory Tract.—Evidence of inflammation of the bronchial mucous membrane is not infrequent in the initial stage of the disease. In fulminating cases passive congestion of the lungs, atelectasis, foci of bronchopneumonia, and interstitial emphysema may be present. Pleurisy with serous, purulent, or sanguinolent effusion has been seen rather frequently in some epidemics.

Lymph-nodes.—Inflammatory swelling of the lymph-nodes in various regions of the body is common

early in the disease. The most frequently affected are the cervical, submaxillary, bronchial, and mesenteric nodes. Suppuration never occurs.

Heart.—The myocardium may show inflammatory and degenerative lesions. Westenhoeffer describes circumscribed or diffuse infiltration of the cardiac muscle, also cloudy swelling and fatty degeneration of the muscle-fibres. In a number of cases these changes have been observed before the onset of meningeal symptoms. Evidence of fresh valvulitis is seen occasionally at a very early stage of the disease. Meningococci were found in vegetations by Weichselbaum and Ghon and Westenhoeffer. In the cases of Warfield and Walker and Cecil and Soper, a meningococcus endocarditis was present, but there were no evidences of meningitis. Acute serous or purulent pericarditis has been seen by a number of observers.

Gastro-intestinal Tract.—In the mucous membrane of the stomach petechiæ may be present. Occasionally hemorrhagic erosions are seen, due, as Busse thinks, to repeated vomiting. Petechiæ in the intestinal mucosa and swelling of Peyer's patches and the solitary follicles are present in most of the acute cases. The constancy and severity of these lesions in his cases led Goeppert to express the opinion that the gastro-intestinal tract may be one of the portals of entry of the meningococcus. From this point of view

the uniformly negative results of Councilman, Mallory and Wright are significant. It is doubtful if the lesions are truly inflammatory in nature. Similar changes are present in a number of other acute infectious diseases. Moreover, Stuart McDonald found such lesions in a monkey in whom meningitis was produced by intradural injection of cerebrospinal fluid from a case of acute meningitis. It is not probable that the meningococcus can pass the stomach containing its normal degree of free hydrochloric acid with its pathogenic powers undiminished.

Liver.—In most cases there is no evidence of inflammation in this organ. The interstitial changes found by Bettencourt and França may have had no connection with the disease.

Spleen.—As a rule, there is no enlargement of this organ. The pulp may be more vascular. The Malpighian corpuscles at times show some degree of enlargement.

Kidneys.—There are no constant changes in the kidneys. The most frequent lesion is an acute degeneration of the kidney, shown by cloudy swelling and fatty degeneration of the epithelial lining of the tubules.

Inflammatory changes in the bladder, seminal tract, and urethra are rare. Pick observed a case of

double empyema of the seminal vesicles in which the meningococcus was readily demonstrable.

Joints.—In most of the cases in which symptoms referable to the joints are seen during life, there are few post-mortem changes. Suppuration is very rare. Neither Westenhoeffer nor Busse met with a case of arthritis at post-mortem. The meningococcus, unlike the gonococcus, almost never produces changes in the periarticular structures.

Skin.—In the purpuric lesions the vessels are dilated; there are small hemorrhages and leucocytic infiltration beneath the epithelium. Meningococci have been found in the herpetic lesions by v. Drigalski and Herford.

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CHAPTER VI

Clinical Types of Meningococcus Meningitis

It is not surprising that there is lack of uniformity among writers as regards the classification of this form of meningitis. Properly speaking, a typical course of meningococcus meningitis does not exist. The irregular features of its epidemiology are seen once more in its symptomatology. Strict adherence to accuracy would limit our clinical description of the disease to an enumeration and discussion of a multitude of individual symptoms and signs. However, to obviate the vagueness of such a mode of treatment we must forego strict accuracy and describe a number of types. We may therefore classify the disease as follows:

1. Ordinary ..... { Acute stage. / Chronic stage.
2. Malignant ..... { Fulminating. / Hyperacute.
3. Mild.
4. Abortive.
5. Intermittent.
6. Posterior-basic.

Ordinary Type.—This is the usual form of manifestation of the disease in the adult and older child.

It occurs sporadically and in epidemics. The duration of the incubation period is from three to five days. The onset is usually abrupt and violent. Exceptionally, the onset is preceded by a short period of general malaise, nausea, loss of appetite, headache and pains in the back, coryza and sore throat. More commonly, however, the patient is attacked in the midst of perfect health by a sudden chill, rapid rise of temperature, severe headache, and repeated vomiting. In childhood the chill is not uncommonly replaced by one or more convulsions. The symptoms of invasion, as can be seen, are in no way characteristic. They are not unlike those seen at the onset of a number of other acute infectious diseases, such as pneumonia and scarlet fever.

After a short period, varying usually from twelve to forty-eight hours, during which a remission of the symptoms seen at the onset may occur, the phenomena characteristic of meningeal involvement appear. It is purely dogmatic, and not in accord with the clinical picture, to speak of successive stages of excitation and depression at this period of the disease.

The earliest truly characteristic symptoms are stiffness of the head and neck, reflected pains in the head, neck, and limbs, and hyperæsthesia along the back of the head and spine. There appears simultaneously a contracture of the hamstring muscles of the

legs, known as the Kernig sign, which is present in almost all forms of meningitis. With the development of the disease the neck rigidity becomes more marked; retraction of the head and more or less orthotonus appear. The head becomes immobile, permitting neither lateral nor anteroposterior movement without great pain. When an attempt is made to flex the head on the chest by lifting it from the pillow, the whole trunk is raised. The spine is rigid, as though composed of one bone. The headache, due to increased intracranial pressure and compression of the nerve-trunk, usually persists throughout the whole course of the disease. It is chiefly localized in the back of the head. Hyperæsthesia is pronounced. The slightest touch, especially of the neck and spine, produces agonizing pain, and in children may elicit piercing cries. The patients are very sensitive to light and sound. In children a coarse intention tremor is often present at an early stage of the disease. Confusion and quiet delirium occur frequently; unconsciousness is rare. Wakefulness is a common symptom. There are frequent periods of restlessness, during which the patient tosses from one side of the bed to the other. The face is alternately pale and flushed, indicating the instability of the vasomotor apparatus. The pupils are usually equal and react sluggishly to light. Attempted flexion of the head produces transi-

tory dilatation. Alternate contraction and dilatation of the pupils is often present (hippus). Transitory strabismus is occasionally seen, but is much less frequent than in tuberculous meningitis. The tongue is dry and coated. The patients usually lie on the side with the legs flexed at the hip and knees. After the third day a number of herpetic vesicles usually appear on the face about the lips and nose. In some epidemics a considerable number of patients show a profuse petechial or purpuric eruption at an early stage of the disease. The temperature is variable and not characteristic. It is often marked by great irregularity and wide fluctuations within short periods of time. The pulse shows considerable variations in rate and character. Bradycardia is much less frequent than in tuberculous meningitis. The respirations are rapid, but not out of proportion to the temperature. There is usually present a well-marked tache cérébrale characterized by early appearance, intensity, and persistence. The bowels are usually constipated. Goeppert, however, has seen a large number of cases in which diarrhœa was a persistent symptom. In a variable number of cases, acute suppurative otitis media develops. Spontaneous rupture of the drum membrane is extremely rare. The spleen is occasionally somewhat enlarged. The urine is often increased in quantity. At times it may contain albumin, but

rarely any other evidences of nephritis. Involvement of the joints is frequent in some epidemics, very rare in others.

The duration and course of the disease are very variable. It may terminate in death, recovery, or the chronic stage of the disease. More than fifty per cent. of the fatal cases die within the first week. In these cases the rigidity and Kernig sign remain unabated or become aggravated. Great prostration develops, with extremely rapid irregular pulse and labored respiration, which is often of the Cheyne-Stokes type. The delirium passes into stupor and coma. Before death general relaxation sets in, and the temperature may rise rapidly to 105° or 106° F. In other cases sudden collapse and rapid fall of temperature may occur, and death takes place unexpectedly within a few hours.

Beginning recovery is usually presaged by reduction of the temperature and diminution of the headache, pains in the back, hyperæsthesia, restlessness, and rigidity of the neck and limbs. The Kernig sign persists for some time after all the other symptoms have disappeared. Recovery usually takes place within from ten to thirty days. At any time within this period sudden exacerbation of the characteristic symptoms may set in. In most of the cases convalescence is uninterrupted and complete.

In a variable number of cases the acute stage

passes gradually and imperceptibly into the chronic stage, which may last from two to six months or longer. Progressive emaciation appears, due most probably to trophic disturbances. The temperature varies markedly. For longer or shorter periods it may be normal or even subnormal. Sudden, irregular accessions of fever may occur from time to time. The mind may remain clear to the end. In other cases mental weakness develops. Adults may become childish and children show no interest in anything but food. Rigidity of the neck and spine and the Kernig sign persist through the chronic stage. Active movements of the limbs become awkward and are often accompanied by well-marked tremor. At times there may be paroxysms of tremor of the arms and legs following excitement or unusual effort. Even in adults there are often in this stage incontinence and retention of urine and fæces. Due to this and the trophic disturbances mentioned above, bed-sores often make their appearance. The most common complication of this stage is chronic hydrocephalus, the symptoms of which will be described in another section. Most of the cases finally succumb to marasmus. Death is often preceded by one or more convulsions. However, even in the apparently hopeless cases recovery is possible. Gradually the rigidity becomes less marked, the febrile attacks less frequent, the mind

more active. Convalescence is extremely tedious, the neck is very weak and unable to support the head fully, and the gait is awkward for a considerable time. The mental power in most of the cases that recover returns in full vigor. The changes in the cerebrospinal fluid will be described in another chapter.

Fulminating Type.—These cases are usually seen in the early periods of an epidemic. They are characterized by intensity of the onset and rapidity of the course. The disease may begin with violent headache, vertigo, convulsive seizure, and high fever. In other cases the onset differs in no wise from an apoplectic attack, the patient passing rapidly into deep coma. There is extreme prostration, with irregular thready pulse, labored irregular respirations, often Cheyne-Stokes in character, and coldness and cyanosis of the extremities. A petechial or purpuric eruption on the chest, abdomen, or extremities appears. The fatal termination usually occurs within from ten to thirty hours after the onset, often before the characteristic symptom of rigidity has had time to develop.

Hyperacute.—These cases, many of which are seen at the height of an epidemic, resemble the ordinary form, but the symptoms are more marked and rapid in their development. The temperature is usually very high, the rigidity of the neck and spine

extreme, and the Kernig sign pronounced. There is marked delirium and restlessness. The pulse is rapid and weak, the respiration labored, and the extremities are cold and cyanotic. A petechial or purpuric eruption is often present, and metastatic foci of suppuration are not uncommon.

Mild Type.—These cases are not infrequent in the declining stage of an epidemic. This type of the disease may attack a large number of individuals in a school, regiment, or village. The onset is much less abrupt. The patients complain of general malaise, anorexia, moderate headache, and pains in the spine and limbs. The temperature may not rise above 101° F. The rigidity of the neck is not very pronounced. At times it simulates an ordinary torticollis. The disease usually runs its course within a week. Convalescence is rapidly established. At times the subjective symptoms are so slight that the patient is able to pursue his work with practically no interruption (ambulatory cases).

Abortive Type.—The onset and early course of the disease differ in no wise from those seen in the ordinary type of the disease. At the end of two to five days, however, there is sudden cessation of all symptoms and convalescence is established. Some of the cases are marked by a number of short relapses.

Intermittent Type.—The fever curve resembles

closely the type seen in tertian malaria. The paroxysms, however, are of longer duration and they do not show the regularity as to time of occurrence which is such a marked feature of malaria. The meningeal symptoms vary in severity, but usually run parallel with the temperature curve. The mildness of the characteristic symptoms of meningeal involvement has often led to the mistaken diagnosis of malaria. The course is usually protracted.

CHAPTER VII

Meningococcus Meningitis in Infancy

Up to within a comparatively recent period, the opinion was quite general that this affection, especially that form which occurs sporadically, was rare in infancy. This is in large part due to the fact that, previous to the general adoption of lumbar puncture as a diagnostic aid, the disease was frequently not recognized. The difficulties encountered in the diagnosis, the high mortality, and the frequent occurrence of serious complications and sequelæ demand a somewhat extended treatment of the infantile forms of meningococcus meningitis.

Fulminating cases occur in the infant as well as in the adult, but, probably on account of lack of characteristic symptoms, more often escape recognition.

The usual type begins abruptly in the infant almost as often as in the adult. At least in the great majority of our own cases there was a definite history of sudden onset. It must, however, be admitted that the French authors, such as Netter and Debré, speak of an insidious onset, with slight fever, listlessness, somnolence, vomiting, and diarrhœa, as the one most common at this age. Rapid rise of temperature, vomiting, and convulsions were present at the onset

of many of our cases. With the development of the disease, three important symptoms make their appearance,—namely, hyperæsthesia, rigidity of the neck, and bulging anterior fontanelle. The hyperæsthesia is at times the one prominent symptom. In a number of cases Goeppert was enabled to make an early diagnosis by this symptom alone. The presence of hyperæsthesia is, according to this author, best demonstrated by moving the legs or attempting to sit up the patient. The rigidity of the neck, though usually present, is occasionally so slight that it must be sought for in a most painstaking manner. To detect the slightest degrees of rigidity, Netter and Debré advise that, at the end of a thorough physical examination, the baby should be placed naked on a flat table, when the slighest retraction of the head or rigidity of the spine becomes more pronounced, as a result of the previous manipulation of the patient.

Tension and bulging of the anterior fontanelle is an important symptom and should always be sought for in febrile babies. Its presence is of especial significance in infants suffering from watery diarrhœa, in whom the fontanelle is, as a rule, depressed. Another symptom of meningeal involvement, which in our experience is constantly present at this age, is the loss of ability to sit up in bed. We have also found a well-marked tremulousness of the hands on active

motion a frequent symptom throughout the course of the disease. The Macewen sign, indicative of increased fluid in the cerebral ventricles, becomes of value only after the fontanelle is closed. The Kernig sign is practically devoid of diagnostic value below two years of age. Restlessness may be present; usually, however, the infants are somnolent and quiet unless disturbed, when they emit piercing cries of pain. Even more frequently than in adults and older children does this form of meningitis in infants terminate in death or in a protracted chronic stage.

TYPICAL CASE.—C. S., age 5 months; admitted May 26, 1903; discharged cured July 9, 1903:

Family and Past History.—Negative.

Present History.—Sudden onset five weeks ago, with general convulsion and high fever (which lasted three weeks). Child vomits two or three times a day; projectile in character. Child sleeps much, but is irritable. Head retracted since onset; bowels constipated. Child has emaciated. Three days ago convulsions recurred, and there have been two per day since then.

Examination.—Child lies quietly in bed; legs drawn up; cries when disturbed. General condition poor. Eyes turned downward, otherwise normal. Anterior fontanelle wide open. Head large and square. Marked opisthotonus, rigidity of neck, and general hyperæsthesia. Kernig present; marked tache cérébrale. Entire right upper extremity held flexed, but there is no rigidity or palsy of any limb. Heart action irregular, rapid. Abdomen slightly retracted.

Clinical Notes.—May 27: Leucocytes 12,000. Lumbar puncture: 45 cubic centimetres fairly clear fluid obtained. Contains meningococci in spreads and cultures. Immediately after puncture eyes were no longer rolled down, but were held in normal position.

May 28: Leucocytes 22,000. Fontanelle bulging.

May 31: Two days ago temperature came down and has remained normal. Apathy continues. Eyes again rolled down. Opisthotonus marked; hyperæsthesia continued. Another lumbar puncture done.

June 3: Fontanelle again bulging; eyes rolled down. Chvostek present. Temperature remains normal. No vomiting.

June 6: Temperature normal for past week. Fontanelle bulging. General condition practically unchanged.

June 8: Third lumbar puncture: 12 cubic centimetres removed.

June 9: Temperature remains normal. Child seems brighter. No more opisthotonus. Slight hyperæsthesia and slight rigidity of neck still present.

June 12: Child brighter. Fontanelle soft. Eyes not rolled down. Abdomen retracted. No hyperæsthesia. Neck very rigid.

June 15: Fourth lumbar puncture: 25 cubic centimetres withdrawn under pressure.

June 18: Temperature normal; pulse regular. Abdomen retracted. Opisthotonus and neck rigidity still present. No hyperæsthesia.

June 21: Child gaining in weight. Seems brighter. No more opisthotonus. Rigidity of neck disappearing. Leucocytes 13,000.

July 8: Fontanelle slightly depressed.

July 9: Fontanelle no longer depressed. Temperature normal. Child has gained weight. No meningitis symptoms. Discharged cured.

Posterior Basic Meningitis.—This form of meningitis, seen almost exclusively in the first two years of life, was first described by Gee and Barlow in 1878 under the name of "cervical opisthotonus of infants." Their observations were based on twenty-five sporadic cases, some of which had a sudden, others a gradual onset. The most striking feature was a "holding back of the head." Other characteristic symptoms were fever, vomiting, convulsions, and rigidity of the limbs. At autopsy a variable amount of purulent exudate at the base and dilatation of the ventricles were found. In 1897 Carr again described a number of cases, and attributed the hydrocephalus which is a frequent complication to two causes,—namely (1) obliteration of the foramen of Magendie, thus preventing the escape of cerebrospinal fluid from the ventricles; (2) compression of the basilar vessels by exudate, sometimes causing a thrombosis of the veins of Galen, thus producing a passive hyperæmia and transudation of serum in the ventricles. In 1898 Still gave an admirable clinical description of this type of meningitis. In seven out of eight cases he succeeded in finding in the exudate of the ventricles

PLATE IV

Posterior basic meningitis, child six months of age. (Koplik.)

FIG. 10.—Posterior basic meningitis, age eleven months.

and subarachnoid space a diplococcus which closely resembled the diplococcus of Weichselbaum. It apparently differed from the meningococcus in growing more readily on plain agar and in broth. On agar it could be kept alive for twenty-four to thirty-four days; on blood agar for fifty-three days. It possessed very feeble pathogenic properties for laboratory animals. Despite these differences, Still expressed the opinion that the germ discovered by him was merely a variety of the meningococcus and not a distinct species. In 1905 Koplik first established the important fact that posterior basic meningitis may occur in epidemic as well as in sporadic form. Among thirty of his cases of epidemic meningococcus meningitis there were eight cases of the posterior basic type.

Pathologic Anatomy (Plate IV).—The pathologic anatomy of this type differs from that of the ordinary adult type in that the primary seat of the inflammation is at the posterior part of the base of the brain,—*i.e.,* where the medulla passes into the spinal cord. A yellow fibrino-purulent exudate fills up the cisterna magna. From this region it spreads downward for a variable distance along the posterior aspect of the cord, inward toward the ventricles, and forward along the base of the brain as far as the

interpeduncular space, the optic chiasm, and the tips of the tempero-sphenoidal lobes. It is often stated that the vertex is rarely involved. Langmead, however, states that in 19 out of 50, or about 40 per cent. of the autopsies at the London Sick Hospital for Children, the inflammation was demonstrable at the vertex, but was never primary there. The ventricles are almost always dilated and filled with clear or turbid fluid.

Clinical Course (Fig. 10).—The disease belongs pre-eminently to early infancy. It is seldom seen in children above two years of age. The youngest patient of our series was four months old, the oldest five years. The onset is usually sudden, with fever, vomiting, and at times a convulsion. After the lapse of several hours or days the characteristic retraction of the head sets in. This feature is so striking that a diagnosis of the condition can be made at a glance. With the retraction there is associated more or less opisthotonus. The arching of the back is at times so pronounced that the head may touch the sacrum. The chest shows marked anterior bulging, while the abdomen is rigid and retracted. The position of the extremities varies. Most often they are found in rigid extension. The hands are pronated and the fists clenched, giving the driving position characteristic

of tetany. The legs are adducted, at times crossed. The foot may show extreme extension at the ankle. In other cases there is flexion of the limbs at the various joints. But whether in extension or flexion the spasticity of the limbs is such that it can not be overcome by permissible efforts on the part of the physician. From time to time relaxation may occur. The slightest disturbance, however, causes immediate reappearance of the spasticity.

The open fontanelles are tense and bulging, and in the younger infants there is often wide separation of the sutures and dilatation of the veins of the scalp. This is due to progressive increase of fluid in the ventricles. The pupils are usually dilated and the upper lids retracted. The resulting exposure of the upper part of the sclera gives the patients a peculiar blank staring look. Strabismus is usually present in the later stages of the disease. About one-third of the patients exhibit some degree of blindness. This symptom is of central origin, as in most of the cases the disks are quite normal.

The patients are apathetic and lie quietly for hours at a time without a movement or sound. Food is devoured greedily. Vomiting is often a very troublesome symptom. It may occur paroxysmally throughout the course of the disease. It is often projectile

in character. The temperature varies markedly. At the onset it may range from 101° to 103° F. for several days or a week. At a later stage it may be normal or only slightly above normal. From time to time the temperature may show wide excursions. Immediately preceding death hyperpyrexia may appear.

Progressive emaciation is a feature equally as constant as the retraction of the head. The patients often become worn to a skeleton. The vasomotor paresis is evidenced by the presence of tache cérébrale and transitory erythemas. The Kernig sign is difficult to obtain because of the rigidity. The Babinski reflex is rarely present. There is usually a slight leucocytosis. It is rarely above 25,000 to the cubic millimetre. In this respect the disease resembles tuberculous meningitis.

Dry taps on lumbar puncture are comparatively frequent. This is attributable either to obliteration of the foramen of Magendie or to adhesions at the base of the brain shutting off the cranial ventricles and subarachnoid space from the spinal canal. In those cases in which a sufficient amount of cerebrospinal fluid is obtained, it is not infrequently sterile. The ventricular fluid on puncture or at autopsy occasionally shows the meningo-

coccus in cases where the fluid obtained by lumbar puncture had previously given a negative bacteriologic result.

Identity of Posterior Basic Meningitis with Meningococcus Meningitis.—The distinctive clinical, bacteriological, and pathological features of this type of meningitis have led a number of British clinicians to assume that posterior basic meningitis is a disease *per se*. There can be little doubt at the present time, however, that it is merely a variety of meningococcus meningitis.

Hunter and Nuttall in seven typical cases recovered organisms from the cerebrospinal fluid obtained by lumbar puncture which were absolutely identical with the diplococcus described by Weichselbaum. Dopter and Martha Wollstein have shown identical agglutination reactions of the two organisms. Moreover, Langmead has demonstrated the similarity in the pathologic anatomy of the two diseases by showing involvement of the vertex of the brain in 19 and exudate in the ventricles in 34 out of 50 cases of posterior basic meningitis. The differences in the clinical picture, the absence of herpes and rashes, and the presence of amaurosis are probably attributable to age. Langmead has shown that in children over 3½ years of age, posterior basic meningitis runs a course very similar to the ordinary type

of meningococcus meningitis, as is shown in the following table:

	Rash.	Temperature.	Optic neuritis.	Amaurosis.
			per cent.	
Posterior basic meningitis in infants	Very rarely	Usually slight; higher and irregular if fatal	3 in 42 = 7 (Barlow and Lees)	At least ½.
Posterior basic meningitis in older children	2 in 10 herpes	8 in 10 irregularly intermittent	5 in 10 = 50	1 in 10.
Cerebrospinal fever	6 in 30 purpuric, 5 in 30 herpes, New York epidemic	No fixed type, but one form intermittent	6 in 40 = 15 (Randolph)	Very rarely.

We are therefore justified in assuming that posterior basic meningitis is a form of meningococcus meningitis seen in a certain number of infants and young children.

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CHAPTER VIII

Symptomatology

Pathogenesis.—In the causation of the multiplicity of symptoms of the disease several factors are involved: First, the local growth of the meningococcus in the meninges and viscera, producing a series of constitutional symptoms; second, decomposition products resulting from the disintegration of nervous tissue, which are thrown into the circulation; thirdly, increased intracranial pressure.

According to Kopetzky, the first effect of the growth of the meningococcus in the meninges is a consumption of the carbohydrate of the cerebrospinal fluid and the production of lactic acid. The increased acidity leads to œdema of the nerve tissue and meninges, and this is further increased by compression of the nutrient vessels. A change in the composition of the fluid results, which leads to an alteration in its tension and permeability, and consequent stasis.

Interference with the metabolism of the cellular elements of the nervous tissue leads to their degeneration and the production of poisonous alkaloids, chiefly cholin, which in turn act as nerve poisons. At a later stage of nerve disintegration neutral fat is formed.

The anæmia which results from compression of the centres in the medulla, as a result of the increased intracranial pressure, acts as a stimulant to the vasomotor centres. The blood-pressure is thus raised, and the anæmia temporarily overcome. The changes in the respiratory rhythm are chiefly due to the alternate increase of intracranial and blood pressure.

Mode of Onset.—In the vast majority of cases the onset is typically sudden. Even in infancy, if sufficient care is taken, a history of sudden onset is usually obtainable. The abrupt mode of onset is not so seldom the only clinical feature which distinguishes this form of meningitis from other meningitides of secondary origin. The French authors describe a fulminating onset in which the disease begins with convulsive seizures, violent delirium, or deep coma, and then develops into an ordinary form of meningitis of moderate severity. Premonitory symptoms, such as general malaise, lack of appetite, and vague general pains, are occasionally present, but are usually of such a mild character that they pass unnoticed by the patient. Still more rare is the occurrence of a coryza, angina, or otitis. The initial stage of the disease is marked by three prominent symptoms,—namely, fever, headache, and vomiting, due to absorption of bacterial products and increased intracranial pressure.

Vomiting at the onset is rarely absent in the adult. It is somewhat less frequent in the infant. In our series of 75 children under 13 years of age, it was present in 61. The frequency seems to increase with age; thus, in children below two years of age, it was present in 20, absent in 10; above two years, present in 41, absent in only 4. Goeppert similarly calls attention to the comparative infrequency of this symptom in patients under three years of age. At this stage it has the character of the vomiting seen at the onset of many acute infectious diseases, and is seldom projectile in type.

Headache is constant in older patients that retain consciousness. It is most often localized in the occipital region, and is of such an agonizing character that the patients often scream with pain and bury the head in the pillow. It is not infrequently associated with pain in the neck and back. At times the pain is situated in the frontal and temporal regions or diffusely over the entire cranium.

Fever is seldom absent in cases with acute onset. Within a few hours it may mount to 104° or 106° F. In the adult it is quite commonly accompanied by a severe chill. In fulminating cases the prostration is at times so great that there is no rise of temperature. An initial convulsive seizure is not unusual in young children. It was present in 12 of 30

infants below two years of age, and in 10 of 45 children between the ages of three and thirteen years. In adults the convulsive stage may be followed by transitory hemiplegia, causing the physician to suspect the presence of cerebral hemorrhage, embolism, or thrombosis. Increase of intracranial pressure at this stage is usually shown by the Macewen phenomenon, or bulging of the anterior fontanelle.

Delirium, usually of a mild character, is another frequent symptom in the initial stage. It is interrupted at frequent intervals by complaint of intense headache.

The characteristic symptoms of meningeal involvement usually appear within twenty-four hours. At times their appearance is delayed for several days.

Temperature.—Unlike typhoid, pneumonia, and many other acute infectious diseases, meningococcus meningitis presents no definite type of fever. In fact, cases are reported in which an afebrile condition was present throughout the whole course of the disease. Such cases are, however, extremely rare. In the initial stage, as we have seen, the fever is usually high. But cases in which the temperature at this stage does not rise above 100° or 101° F. are not at all rare. At times the temperature drops to normal on the day after the onset. It may then remain normal for two or three days and then rise again.

More frequently, however, the temperature shows continuous elevation for three, four, or five days (Fig. 11). In some cases the temperature is continuous, with remissions of not more than one degree, resembling the typhoid curve of the fastigium. In others regular daily remissions of two or three degrees may be seen, giving the spiked curve of the

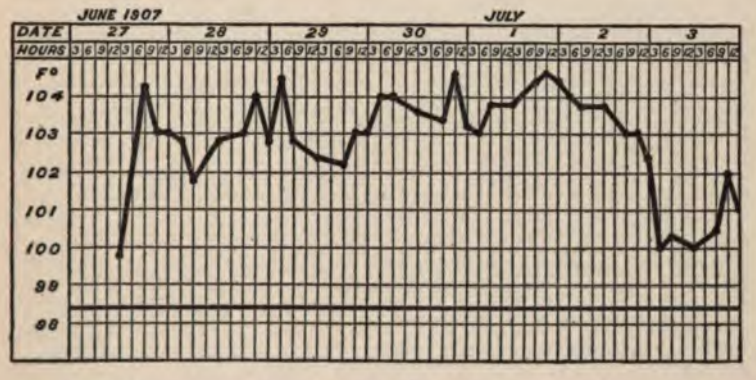


Fig. 11.—Epidemic cerebrospinal meningitis. Ordinary temperature curve.

third week of typhoid (Fig. 12). In the intermittent form, regular intermissions and exacerbations occur, accompanied by chills. The paroxysms are usually distinguishable from those of tertian malaria by their more prolonged course. In the more protracted cases remissions and exacerbations occur irregularly, as in pulmonary tuberculosis. The temperature in the moderate cases often falls by lysis at the end of six or eight days. After the injection

of antimeningitis serum, there occurs in about 30 per cent. of the cases a critical fall of the temperature. There is no constant parallelism between the temperature and the condition of the patient or the intensity of the other symptoms. The effect of lumbar puncture on the temperature is usually evident. It causes either a fall or rise (see Chart I). Imme-

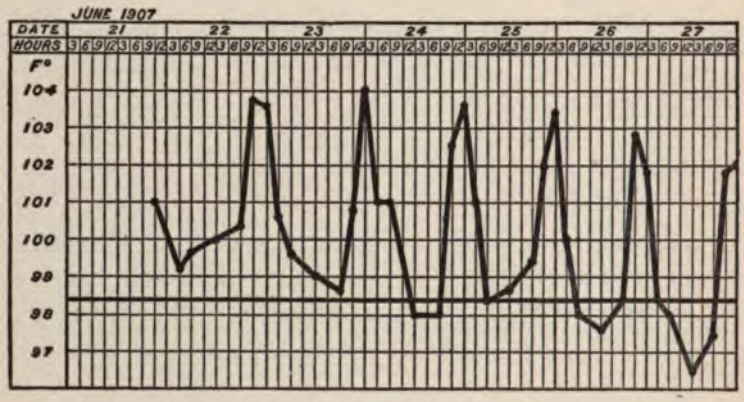
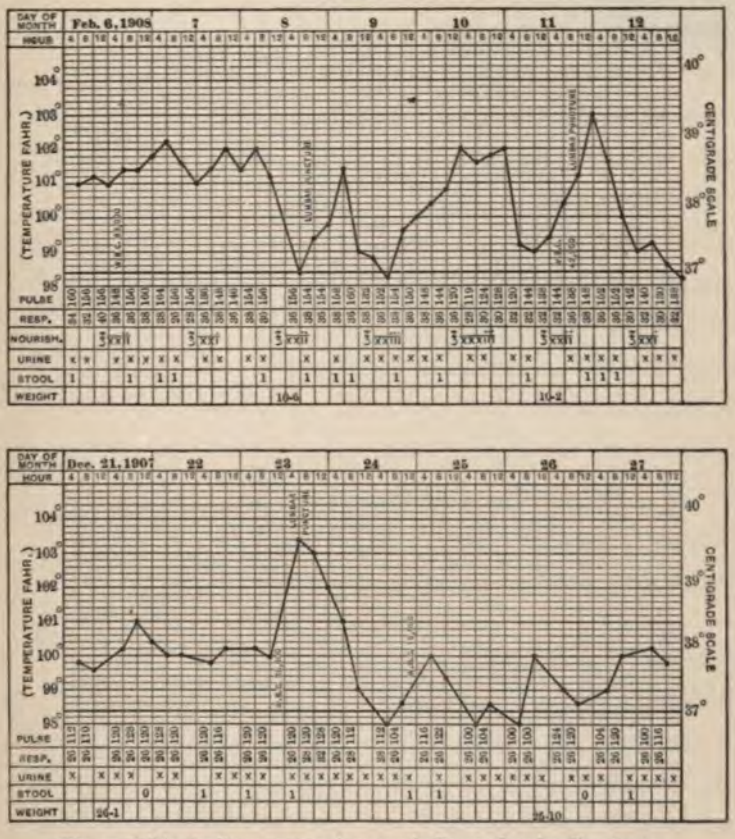


Fig. 12.—Intermittent temperature curve.

diately before death, in acute as well as chronic types of the disease, the temperature rises rapidly to 105° or 106° F.

Pulse.—The pulse is usually rapid, but not out of proportion to the temperature. There is seldom seen the bradycardia which is so pronounced a characteristic of tuberculous meningitis. The instability of the vasomotor apparatus is shown by sudden and un-

CHART I



Rise or Fall in the Temperature Apparently Due to Lumbar Puncture.

accountable changes in the rapidity and character of the pulse. In the course of a single examination the pulse-rate may vary from 60 to 130 per minute.

Respirations.—In the initial stages of the disease in infants, the respiratory rate is often markedly increased (60 to 70 per minute) without there being any physical signs in the chest. At a later stage this disproportionate rapidity of the respiration disappears. At one time or another, and especially in the severer cases, the respirations become irregular. The irregularity is, however, rarely as pronounced as in tuberculous meningitis. According to Conner and Stillmann, who have made a careful pneumatographic study of the respiratory irregularities in meningitis, they are present in 95 per cent. of the cases. Three forms of irregularity may be present,—namely, Cheyne-Stokes respiration, the Biot respiratory type, and undulatory type.

In the Cheyne-Stokes type there are rhythmical alternations of periods of respiratory movements with periods of apnœa. The respiratory periods are of approximately equal length and composed of the same number of individual respirations. The duration of the pause equals ½ to ¾ of the respiratory period. In infants and young children, the duration of each is much less, and the number of respirations making up the respiratory period much smaller. The

period of apnœa is relatively longer, being about equal in duration to the respiratory rhythm.

Biot first described the type of respiration named after him in 1876, and more elaborately in 1878. It has the following characteristics:

Periods of apnœa of varying lengths, occurring at irregular intervals.

Constant irregularity in rhythm and force of the individual respirations.

Frequent deep sighing respirations. (This is a striking feature of the Biot type.)

Conner and Stillmann found the Biot type twice as frequently in the adult as in the child, while the Cheyne-Stokes type was seen by them twice as often in children.

In the undulatory type no periods of apnœa are present, but there are wave-like variations in the depth of inspiration, muscular tonus, or frequency of respirations.

Very few of the meningitis patients failed to show this type at one or another time. The Biot type is most pathognomonic of meningitis. It is, however, seen only in the very grave cases. The presence of Cheyne-Stokes respiration in children is strongly suggestive of meningitis.

General Appearance and Attitude.—The face is usually flushed and the expression often bright and

anxious. Young patients show signs of suspicion or anxiety, due to the fear of being disturbed. This is in marked contrast to the "absent" look seen frequently in tuberculous meningitis. Evanescent flushing or pallor of the face due to vasomotor instability is often observed in the various stages of the disease. The conjunctivæ are usually clear, occasionally suffused. The patients lie on the side, as in this position there is less pressure on the back of the head. When prostration is marked and coma supervenes, the patients often lie relaxed on the back.

Mental Condition.—In contrast to other forms of meningitis, tuberculous meningitis in particular, the mind is at times perfectly clear. Even during periods of confusion the patients can be aroused sufficiently to answer questions fairly intelligently. Loss of consciousness in children below three years of age is rare. Marked restlessness and irritability are frequent in this type of meningitis. The patients often toss about for hours at a time. Insomnia is an annoying symptom of great frequency, and is partly due to the headache which shows nocturnal exacerbations. Paroxysmal delirium is frequent. It is often of a mild grade; at times, however, it becomes maniacal in character. At the terminal stage and in malignant types of the disease, the patients fall into deep coma. The chronic stage of the disease is

marked by apathy, lack of interest in the surroundings, and at times stupor. The last symptom usually develops with increasing hydrocephalus.

Ocular Symptoms. — The frequency of these symptoms varies greatly with each epidemic. It is probable that in the past these symptoms have frequently been overlooked, as they are often present only during a short period of the disease.

The following table, taken partly from Goeppert, gives the observation of a number of clinicians who have paid special attention to this phase of the symptomatology of the disease:

	Uthoff (160 cases).	Heine (160 cases).	Goeppert (150 cases).	Ballantyne (73 cases).
	p. ct.	*p. ct.*	*p. ct.*	*p. ct.*
Changes in pupils.....	12 = 11	.....	37 = 24	63 of 69 = 91
Disturbances of ocular muscles.....	16 = 15	7 = 7	17 = 12	23 = 31
Nystagmus.....	8 = 7	3 = 3	.....	7 = 9+
Optic neuritis.....	18 = 16	8 = 8	.....	5 of 61 = 8

Changes in the Pupils.—These are the most common of the eye symptoms of the disease. Inequality of the pupils is very frequent in the first few days. More or less mydriasis is present in more than half of the cases during the height of the disease. The size of the pupils changes greatly from time to time. Myosis is usually present during a convulsive seizure. Rhythmic changes in the pupils which are

independent of the illumination or distance of the focused object (hippus) are frequently seen. We have often observed sudden dilatation of the pupils when the attempt is made to flex the head on the chest. In severe cases Goeppert has observed dilatation of the pupils on irritating the skin. Its presence in the earlier stages of the disease he considers to be of grave omen. In deep coma the light reflex is frequently lost.

Disturbances of the Ocular Muscles.—Strabismus is the most common of these disturbances. Goeppert is of the opinion that unilateral convergent strabismus is present at one time or another in one-third of the cases during the first three days of the disease. In our own cases strabismus was present in 12 of 30 infants below two years of age, and in 22 of 45 children between three and thirteen years of age. Unlike that of tuberculous meningitis, the strabismus is rarely paralytic in nature. It varies greatly from time to time; occasionally a convergent is changed directly into a divergent squint. Nystagmus seems to occur more frequently in severe cases. It was present in 9 of 75 of our patients. At times conjugate deviation of the eyes is present. This symptom is often observed during and after a convulsive seizure.

Optic Nerve Changes.—Optic neuritis is much

less frequent than in tuberculous meningitis. In our cases it was rather unusual to find marked changes in the disk during the acute stage of the disease. Similarly Matthes found no changes in the fundus in 35 cases. According to Netter and Debré, papillitis is frequent at the height of the disease. It is bilateral and usually of short duration. In most of the cases they did not observe any change in the acuity of vision.

Sensory Disturbances.—The most frequent subjective disturbances are headache, hyperæsthesia, and pains in various parts of the body. In the acute stage the headache is almost constant, though marked by nocturnal exacerbations. At times the torture produced by this symptom is almost unendurable. On its appearance, otherwise stoical individuals often cry like babies or attempt self-destruction. The site of the pain varies; most often it is localized in the occipital region. In the chronic stage it is not infrequently paroxysmal in character and is accompanied by elevation of temperature and vomiting.

Hyperæsthesia is a cardinal symptom, rarely absent in conscious patients. They are very sensitive to light and to loud sounds. Ker observed in many patients an extraordinary sensitiveness to cold. The hyperæsthesia is most pronounced along the spine and is often much relieved by lumbar puncture. In

young children Goeppert has observed a series of cases in which hyperæsthesia of the lower extremities on passive motion was an early and pronounced symptom.

Spontaneous pain in the extremities is often present. It is in part due to pressure of the inflammatory exudate on the spinal roots. It may be felt as shooting pains along the course of the nerves. In other cases it is localized in the muscles or joints. Despite the marked rigidity of the spine, spontaneous pain in this region is rarely very severe. At times reflected pain is present along the front of the neck, thorax, and abdomen.

Motor Disturbances.—Convulsions are rare in the adult. Typical epileptiform attacks may, however, be seen in grave cases. At times status epilepticus develops, leading rapidly to a fatal termination. In rare cases paroxysmal attacks of tetany occur, with spasmodic retraction of the head, marked opisthotonus, rigid extension of the arms, and clenching of the fists. Tremor of the hands from the earliest stages of the disease was often observed by us in young patients. Twitching of the lids, athetoid movements, munching and sucking motions, spasmodic shaking of the head, subsultus tendinum, and carphologia are occasionally seen in children.

Reflexes.—The deep reflexes are at times difficult

to obtain, on account of the hyperæsthesia and rigidity of the limbs. The knee-jerk was present in 21 and active in 15 of the 45 cases between three and thirteen years of age. The superficial reflexes are usually preserved in the early stages of the disease. Both the deep and superficial reflexes usually disappear in the rapidly fatal or moribund cases. Ankle-clonus was never observed by us.

The Babinski reflex (Fig. 13), (extension of the great toe following irritation of the plantar surface of the foot) is of little value in children below two years of age, as it is often seen in perfectly normal infants. It was present on one or both sides in 24 out of 45 children above two years of age. Other observers have found it rather less frequently. At any rate, it occurs less often than in tuberculous meningitis, where Koplik found a positive reaction in 77 per cent. of his cases.

The Oppenheim reflex (extension of the great toe following vigorous rubbing along the inner surface of the tibia) is apparently much less frequent in these cases than the Babinski, as it was present in only 2 out of 45 of the older children.

Vasomotor and Trophic Disturbances.—Tache cérébrale is seen frequently, but is not of very great value in diagnosis. When the nail is drawn across the skin, there appears a red line having no definite bor-

FIG. 13.—Babinski sign.

ders or one limited on each side by a white line. In meningitis it is characterized by the rapidity of its appearance, intensity, and persistence. In the course of the disease the skin often becomes suddenly flushed or covered with perspiration. Evanescent localized erythema also occurs quite frequently. The progressive emaciation, which is so constant and striking a feature of the cases running a chronic course, is due for the most part to trophic disturbances.

Rigidity of the Neck.—This is the cardinal symptom of meningeal irritation or infection. It is present to a greater or less extent in nearly all forms of meningitis. In very young or very old patients, and in those who are in a condition of collapse or deep coma, rigidity of the neck is likely to be absent. To detect slight degrees of rigidity, the head should be placed in the hollow of the hand and moved gently in all directions. It is of the utmost importance in children not to mistake voluntary resistance for true rigidity. Voluntary resistance of the neck varies from one moment to another and is apt to disappear in the course of a single examination. True rigidity, on the other hand, usually becomes more pronounced with the repetition of the manipulations employed for eliciting it. Moreover, it gives the experienced examiner the impression as though the cervical vertebræ were soldered together. To acquire skill in the

detection of slight degrees of rigidity constant practice in the examination of many sick and healthy infants is essential.

With the advent of specific serotherapy and the supreme importance of its early employment in the proper cases, the detection of the earliest traces of rigidity becomes a matter of the greatest moment. On its demonstration often hinges the sole indication for the diagnostic procedure of lumbar puncture.

It is equally important to remember that in some cases the rigidity is not present at all times. Frequent examination for this symptom is therefore necessary in cases where the slightest suspicion of the presence of meningitis is entertained. The accentuation of this symptom at the end of repeated manipulations at times permits its visual detection if the patient is completely uncovered and placed on a flat surface. Rigidity of the neck was present at one time or another in 26 of 30 infants below two years of age, and in 43 of 45 children between the ages of three and thirteen years. Goeppert describes a number of cases in young infants in which this symptom was absent during the whole course of the disease. In contrast to the marked Kernig usually present in old people, the rigidity of the neck is slightly marked or entirely absent. In the stormy course of the cases belonging to the fulminating type,

Fig. 14.—Kernig sign.

Fig. 15.—Kernig sign.

Fig. 16.—Brudzinski signs.

death may take place before this symptom has had time to develop.

The Kernig Sign (Figs. 14 and 15).—This sign, which was first described by Kernig in 1882, shares equal importance with the neck rigidity as a diagnostic feature of the disease. It is present to a more or less marked degree in all forms of meningitis. By itself it is not a pathognomonic sign of meningeal inflammation, as it is occasionally present in meningeal hemorrhage as well as in acute febrile diseases accompanied by meningeal irritation or so-called meningism. In the opinion of a number of authorities, the Kernig sign appears somewhat earlier than the rigidity of the neck. This, however, may be due to the fact that the Kernig sign, even when only slightly marked, is more readily recognized than slight degrees of rigidity of the neck.

The test, as originally described by Kernig, is carried out as follows: The patient is propped up in bed in the sitting posture with the thighs flexed at a right angle to the abdomen. When the sign is present, the legs will be found flexed at the knees, and reasonable attempts by the physician at complete extension at the knees will fail unless the back of the patient is lowered and the angle at the hip thus made more obtuse. On account of the difficulty often encountered in this disease in sitting the patient up in

bed, Osler has proposed a useful modification of the method of carrying out the test. It consists in flexing the thighs on the abdomen at a right angle while the patient is lying in bed in the horizontal position. When the sign is present, complete extension of the legs at the knees is impossible. Another variation of this test consists in the determination of the degree of angular flexion obtainable at the hip with the leg in complete extension at the knee. In cases where the sign is present, this angle under the conditions of the test is never less than 90°. These modifications are now generally employed in America, and seem to yield results which are practically identical with those obtainable with the test carried out according to the original directions of Kernig.

Unfortunately, this important sign is of practically no value in children below two years of age. This is attributable to the rigidity of the legs which is usually present at this age and to the fact that in normal infants there often exists a physiologic myotonia which may yield a positive Kernig sign. The Kernig sign was present in 37 of 45 children above two years of age. This sign, when present, is almost always bilateral. It at times persists long after all other symptoms have disappeared. Goeppert relates a case where it persisted in a marked form as the only symptom for twenty-eight days after convalescence was apparently complete.

While a number of hypotheses have been advanced in explanation of this phenomenon, none that is adequate is at hand. It can not merely be due to increased pressure in the subarachnoid space, as it often persists after lumbar puncture. The most probable explanation is that it is due to irritation of the nerve-roots which leads to contracture of the flexor muscles of the legs. As normally when the thigh is flexed on the pelvis, and the leg extended fully at the knee, these muscles are stretched to the limit of their elasticity, a slight contracture becomes readily evident.

Brudzinski Neck and Leg Signs (Fig. 16).—In 1908 this observer described the presence in meningitis of a sign which he called the contralateral reflex. On passive flexion of the leg on one side, there is either flexion of the other leg (identical contralateral reflex) or extension of the other leg (reciprocal contralateral reflex). In 1909 the same observer described the neck sign which is shown in flexion of the legs on passive flexion of the head and neck. In 42 cases of meningitis, Brudzinski found the neck sign in 97 per cent., the contralateral leg reflex in 66 per cent., while the Kernig was present in only 57 per cent. of the cases.

Greco and Zaimovsky confirmed the observations of Brudzinski. Greco was unable to detect it in conditions other than meningitis, while Zaimovsky

found it almost constant in this disease. In 400 children either perfectly well or suffering from disease other than meningitis, Morse did not find either the neck or leg signs. In meningitis this observer found the neck sign more frequent than the leg sign. It is, however, present in all forms of meningitis, and is consequently of no value in the differentiation between the various forms of this disease. Its absence, on the other hand, does not exclude the existence of a meningitis.

Brudzinski attributes the neck sign to muscular hypertonus of the legs and to physiologic predominance of the extensor muscles of the neck and back over the flexor muscles of the legs. The contralateral leg sign is attributed to a reversion in meningitis to an earlier state of fetal life in which there exists bilateral innervation and anatomical connection between the centres of corresponding muscles of each leg.

Opisthotonus.—This symptom occurs in about 70 per cent. of juvenile patients. In the adult it is much less frequent. It produces arching of the back so that the two points of contact with the bed are the occiput or vertex and the lumbosacral region. When the hand is placed under the head, the whole body moves in a statuesque condition. As has been seen, opisthotonus is a prominent symptom of posterior basic

meningitis and is chiefly instrumental in the production of the characteristic deformity of the disease. As Busse has suggested, this symptom is probably due to the fact that when the back is arched the capacity of the subarachnoid space is increased. This seems to be borne out by the common observation that, when the head, neck, and back are flexed during lumbar puncture, the flow of cerebrospinal fluid tends to increase.

Retraction of the Head.—Retraction of the head is not very common in the adult patient. It is more frequent in children, and is a constant and pronounced feature in cases belonging to the posterior basic type.

Rigidity in other parts of the body occurs much less frequently. Occasionally rigid contraction of the upper extremity is seen. Still more rare is contracture of the masseters producing trismus, or contractures of the facial muscles causing risus sardonicus. At times spasmodic contraction of the muscles of the extremities produces a picture closely simulating the characteristic attitude of tetany.

Fontanelles and Sutures.—The condition of the anterior fontanelle in young children is of the greatest diagnostic importance. In the early stages of the disease it is often tense and bulging; in the second and third week, however, it becomes depressed, even

in those cases that later end fatally. With the bulging of the fontanelle there is not infrequently associated a separation of the sutures. This symptom Goeppert found in 13 of 34 infants. At times the heightened intracranial pressure leads to a reopening of the posterior fontanelle. There is occasionally overriding of the occipital by the parietal bones, due to the greater mobility of the latter. With a high grade of hydrocephalus, the veins of the scalp become dilated and prominent.

Macewen Sign.—In conditions in which there is accumulation of fluid in the lateral ventricles, Macewen has shown that percussion over the anterior horn of the ventricle yields a hollow note. The sign is best obtained by sitting the patient upright and inclining the head to one side, thus placing the inferior portions of the frontal or parietal bones directly under the anterior horn of the ventricle. As it indicates fluid under tension, the sign is manifestly not to be expected in infants that have still open fontanelles. It was present in 35 of 45 children above two years of age.

Gastro-intestinal Disturbances.—Vomiting, as we have observed, is practically always present in the adult and older children at the onset. It appears unexpectedly and is seldom preceded by nausea. The vomitus consists of undigested food or yellow fluid.

In this form of meningitis it is less often projectile than in tuberculous meningitis. It usually disappears soon after the onset, and does not recur except in the protracted cases; in these, paroxysmal attacks of vomiting occur from time to time. In some cases it becomes a serious symptom, as it interferes seriously with the taking of food. In the great majority of meningitis patients the bowels act normally. Occasionally constipation is present; still less often does persistent diarrhœa occur. In infancy the disease may begin with abdominal pain and diarrhœal stools. The appetite, as a rule, is good. The patients often exhibit marked thirst throughout the disease.

Cutaneous Manifestations.—These vary markedly with the character of the epidemic. In the early epidemics in America the rash was so prominent a feature of the disease that it went commonly under the name of " spotted or black fever." The epidemics in Ireland and Sweden were also characterized by great frequency of the rash. In the recent epidemic in New York, however, skin eruptions were generally absent.

Herpes occurs even more frequently in this disease than in pneumonia. It is, however, rare in patients under two years of age. It was present in only 1 out of 30 patients, whereas amongst 45 children above two years of age it occurred in 12 cases.

Between the second and sixth days of the disease Goeppert found herpes in 60 per cent. of the children, but not once in children under three years of age. According to Einhorn, the herpetic eruption of this disease is characterized by great severity, wide distribution, unusual localization, occurrence in crops, prolonged duration and slow healing. It is rarely seen before the second or third day of the disease. Most often it appears at the end of the first week. Its site is variable and it may cover a comparatively large surface of the body. As in pneumonia, it occurs most frequently on the face about the lips and nose. It has, however, been seen on the tongue, gums, palate, conjunctivæ, ends of the fingers and toes, vulva and anal region. As a rule the vesicles are small, but occasionally giant forms may be seen. In one case at the hospital the presence over an extensive area of a number of vesico-pustules aroused for a time suspicion of the existence of variola. Occasionally extensive ulceration occurs. Typical herpes zoster is but seldom seen.

A sparse roseolar eruption, not unlike that seen in typhoid fever, occurs in a small proportion of the cases in the first few days of the disease. In the second and third weeks a more wide-spread morbilliform or scarlatinaform eruption is occasionally seen. They usually occur on the flexor aspects of the extremities and the lower abdomen, and fade rapidly.

Hemorrhagic rashes occur either in the form of a petechial or purpuric eruption. On the first few days they are usually seen on the abdomen, thorax, and inner aspect of the thighs, as numerous small spots resembling flea-bites or larger blotches with indefinite borders, maroon or purple in color. At times there is œdematous infiltration of the overlying skin. In severe cases large subcutaneous hemorrhages may appear, at times associated with hemorrhages in the kidneys, intestines, thorax, and joints. In the terminal period of the chronic stage, the abdomen may be covered with dark red hemorrhagic blotches, varying in size from a millet-seed to a hemp-seed.

Petechiæ are more common in older children than in infants. Recently, however, several infants with petechiæ were admitted to the Mt. Sinai Hospital. In children above two years of age petechiæ were encountered in about 16 per cent. of the cases.

Osler has described a peculiar diffuse livid erythema about the extensor surfaces of the joints of the extremities which was accompanied by vesicles filled with blood. After the erythema faded and the vesicles dried, small nodules persisted for a week or ten days.

The Urine. — Albuminuria, casts, and renal elements are not frequent. Among 66 cases, a heavy trace of albumin and casts were present in 2, faint

trace of albumin in 3; in all the others the urine was chemically and microscopically negative. Hæmaturia, invariably associated with purpura, is at times present in malignant cases. The French observers, Loeper and Gouraud, describe a urinary syndrome or meningitic diabetes characterized by polyuria and increased excretion of nitrogen, phosphates, and chlorides. They attribute this condition to probable irritation of the floor of the fourth ventricle.

The Blood. — An unmistakable polynuclear leucocytosis is a well-nigh constant feature in this disease. It is present in mild as well as in severe cases during the acute stage, and usually also in the chronic stage. The degree of leucocytosis offers no prognostic data of importance, as it often varies unaccountably from day to day. The following table shows the average leucocyte count in our patients below fifteen years of age.

	Below 2 years of age.	Above 2 years of age.
9,000 per cubic millimetre.....	2 patients	1 patient
10–15,000 per cubic millimetre.....	3 patients	4 patients
15–20,000 per cubic millimetre.....	7 patients	9 patients
20–25,000 per cubic millimetre.....	5 patients	13 patients
25–30,000 per cubic millimetre.....	4 patients	8 patients
30–40,000 per cubic millimetre.....	1 patient	4 patients
40–50,000 per cubic millimetre.....	1 patient	4 patients
50–60,000 per cubic millimetre.....	.....	1 patient
60–70,000 per cubic millimetre.....	1 patient (63,000)	1 patient (73,000)

The minimum leucocyte count was 9000 per cubic millimetre, the maximum 63,000 and 73,000 per cubic millimetre.

In fulminating cases the eosinophiles regularly disappear from the blood. The presence in the blood of meningococci, specific agglutinins, and high opsonic index will be discussed in the chapter on Diagnosis.

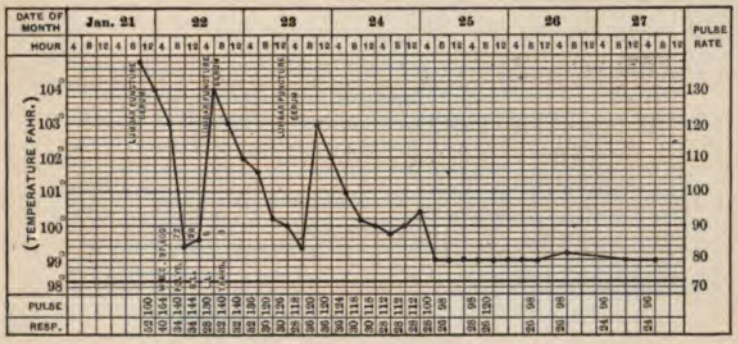
Blood-pressure.—Robinson found a moderate increase in blood-pressure in the early acute stage, during an exacerbation, and at an advanced stage of the disease. There is usually a fall of blood-pressure after lumbar puncture, but the effect of this procedure on the pressure is not constant. During convalescence the blood-pressure, as a rule, is low. With obliteration of the foramina of the fourth ventricle and the development of hydrocephalus, the blood-pressure increases with the increase in intracranial pressure.

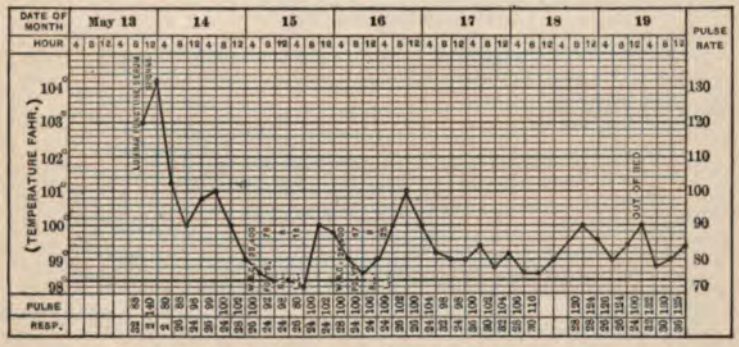
Relapses.—Relapses are quite common and may appear after the lapse of a considerable period of normal temperature and complete absence of acute symptoms. Ker has seen relapses in 15 to 20 per cent. of his cases. On the other hand, Goeppert contends that true relapses are rare. Among 136 convalescents he saw this condition only twice. But he does not consider a patient convalescent until the Kernig,

ankle-clonus, and change in disposition have disappeared. In the literature cases are reported in which relapses have occurred as late as four months after the acute disease. It often appears suddenly without any apparent exciting cause. There may be a repetition of all the initial symptoms. Fever, headache, rigidity, and even herpes may appear once more. These symptoms usually disappear in a few days. With repetition of relapses the case may assume a chronic course. While in most cases the relapse is milder than the original attack, cases are not at all rare in which fatal relapses have been seen.

Convalescence.—The character of the convalescent period has fortunately changed since the adoption of serotherapy, and the description in the older books no longer applies to many of the cases. Formerly it was often extremely tedious. Since the inauguration of specific therapy it is not infrequently surprisingly rapid. Quite often there is a critical fall in the temperature and most of the other symptoms; the headache, hyperæsthesia, irritability, and sleeplessness disappear within a few days. The rigidity of the neck, and particularly the Kernig sign, persist for perhaps a week or more. On first getting out of bed the patient may complain of stiffness in the lumbosacral region and the gait may be awkward and stiff.

CHART II





Critical Fall in the Temperature Caused by Serum Injections.

Recovery from the chronic stage takes place very slowly. The muscles of the neck show temporary paresis, the patient being unable to hold up the head in the sitting posture. General feebleness and emaciation persist for many weeks. The patient may exhibit a train of psychic symptoms. Temporary forgetfulness and loss of mental concentration are often present in adult convalescents. Children quite frequently become peevish and suffer from sudden fits of unprovoked anger. These symptoms will be described in greater detail in the section devoted to the Sequelæ of the disease.

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CHAPTER IX

Cerebrospinal Fluid

Lumbar Puncture.—Before describing the characteristics of the cerebrospinal fluid in health and disease, we must enter into a somewhat detailed description of the important procedure of lumbar puncture. This was first performed by Corning in 1885. His aim, however, was to inject various drugs in the subarachnoid space. It was Wynter, according to Haynes, who first proposed the use of this procedure for the relief of increased intracranial pressure in tuberculous meningitis. He performed this operation upon a patient in the comatose stage of this disease on February, 1889, twenty-two months before Quincke. He made a very small incision along the spine of the second lumbar vertebra, introduced a Southey tube and trocar until the lamina was reached, then directed the trocar slightly downward and inward through the ligamentum and theca. On withdrawing the trocar clear fluid at once appeared. By attaching a fine india-rubber tube provision for continuous drainage was made.

The present technic of lumbar puncture, however, is based entirely on the careful experiments and explicit directions of Quincke. This operation was

first performed by him on December 12, 1890, in a case of marked hydrocephalus complicating an acute cerebrospinal meningitis. His admirable studies soon led to the general adoption of this procedure in the diagnosis and treatment of a number of affections of the meninges and central nervous system. This minor and generally harmless operation enables us in the vast majority of the cases to make an exact etiologic diagnosis of the various forms of primary and secondary meningitides. The omission of this procedure (in the absence of a post-mortem examination) deprives the report of any cases of meningitis, no matter how clear it may be clinically, of scientific validity.

Anatomical Considerations and Landmarks.—The subarachnoid space is situated between the arachnoid membrane and the pia mater of the brain and spinal cord. At the lower part of the spinal canal there is present a spacious cul-de-sac, which surrounds the spinal nerves forming the cauda equina. This space, as we have seen, communicates with the centricular system of the brain by means of the foramen of Magendie, situated at the inferior boundary of the roof of the fourth ventricle, and the two foramina of Luschka, found along the lateral aspects of the covering of the fourth ventricle. Up to the first year of life the spinal cord extends slightly beyond the

lower level of the third lumbar vertebra, but, owing to the relatively rapid growth of the vertebræ, it gradually recedes from the lower part of the lumbar spine and in adults does not reach below the first lumbar vertebra.

Lusk, in a series of fifteen dissections, has very carefully studied the relation of the arachnoid membrane to the posterior surface of the cord and the anatomical features of the cauda equina. He found the conus medullaris (the terminal portion of the cord) at the level of the first lumbar vertebra in 11 cases, at the junction between the twelfth dorsal and first lumbar vertebra in 3 cases. In one case it reached the level of the lower border of the second vertebra. The posterior arachnoid in all but one of the cases did not present a continuous channel, but was either adherent to the posterior surface of the cord or broken up by transverse septa. The free circulation of the cerebrospinal fluid was effected by means of lateral communications with anterior subarachnoid space over the concavities of the ligamentum denticulatum. In some of the cases, in order to obtain fluid by puncture in the middle line at or above the conus, the substance of the cord would have had to be traversed and the fluid derived from the anterior subarachnoid space.

The Nerve-roots at the Cauda Equina.—The

nerves arise serially from the conus, the first lumbar root being most lateral, the lowest sacral occupying the most mesial position. A slight cleft is usual between the lowest sacral nerves of each side. Their mesial position and consequent exposure to traumatism explain some of the cases of paralysis of the bladder and rectum which have followed lumbar puncture. Delicate adhesions usually bind the nerve-roots of the cauda equina in masses. In 7 out of 15 dissections, the nerve-roots were massed together against the anterior subarachnoid space. In some the nerve-roots were either distributed peripherally around the walls of the arachnoid or in relation to its posterior surface. Adhesions of the roots to the latter were present in some of the dissections. The retarded flow of cerebrospinal fluid through the needle, as is seen occasionally, is probably due to the picking up of a nerve-root in the line of puncture. This is best avoided by a mesial puncture in the fourth lumbar space with a needle not too sharply pointed with the nerve-roots relaxed by sacral extension. The space below, the lumbosacral space, is second in order of desirability, as at this level adhesion of the nerve-roots to the posterior wall of the arachnoid sac is more likely to occur, and the subarachnoid cul-de-sac is shallower at this level.

The fourth lumbar interspace, the site of election

for lumbar puncture, is found at the level of a line connecting the highest points of the iliac crests (Fig. 17). There are a number of anatomical factors which contribute to the ease with which puncture is

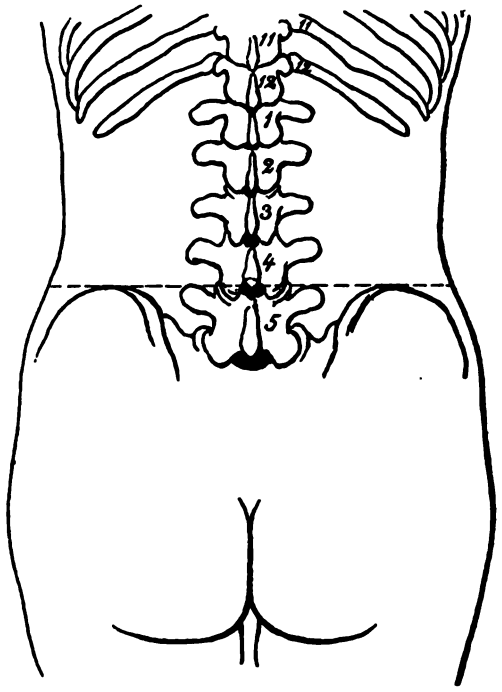

FIG. 17.—Anatomical landmarks for lumbar puncture.

performed in the lumbar region: first, the spinous processes of the lumbar vertebræ are short, thick, and widely separated from one another; second, the long or anteroposterior axis of the lumbar spines has but a slight angular elevation, so that the general direc-

tion of the interspinous spaces is almost at a right angle to the long axis of the spine. The supraspinous and interspinous ligaments in the lumbar region are, however, broad, thick, and tough, and in adults not so readily penetrable by the puncture needle.

The fourth is the space of election, as it is invariably below the level of the conus, and there is least likelihood of injuring the nerve-roots.

Instruments: The Quincke Needle and Manometer (Fig. 18).—The older methods of employing a syringe needle or cannula and trocar, with or without a handle, are no longer in vogue. The latest model of a lumbar puncture set, made by Beckman, of Kiel, according to Quincke's directions, consists of (1) three needles of different lengths and diameters, with corresponding stilettes; (2) a glass manometer tube; (3) rubber tubing and coni for connecting the needles with the manometer; (4) a glass graduate for collecting and measuring the cerebrospinal fluid; (5) a cylindrical glass funnel to be connected with the puncture needle with rubber tubing for the injection of serum. In order to secure uniform pressure determinations, it is advisable to connect the needle with the manometer by means of a piece of catheter tubing, number 5, forty to sixty centimetres long. Sterile test-tubes should be used for collecting

and measuring the fluid. The pressure is measured by means of a piece of steel tape graduated in centimetres and inches.

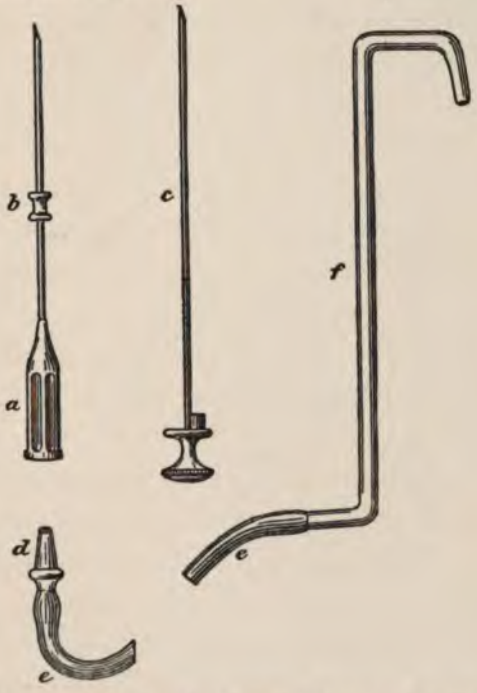

FIG. 18.—*a*, cannula; *b*, guard; *c*, stilette; *d*, conus; *e*, rubber tubing, *f*, manometer tube. Half natural size. (After Quincke.)

The needles measure from four to ten centimetres in length and from .8 to 1.6 millimetres in diameter. The distal extremity of the needle is bevelled at an acute angle to a sharp point, forming connection with the end of the stilette when the latter is *in situ* flush with the end of the needle. The manometer tube is

fourteen centimetres long and two and a half centimetres in diameter.

One of us (Heiman) has had constructed a flange-like movable guard for the needle (Fig. 18), to be set before puncture at a distance from the point of the needle corresponding to the probable depth of insertion. The object of this appliance is to prevent too deep an insertion of the needle, which sometimes results in hemorrhage from the venous plexus in the anterior wall. The guard also serves to steady the needle while in the canal.

Kroenig's Apparatus.—In cases where there is suspicion of the existence of a tumor at the base of the brain, in which the withdrawal of any considerable amount of fluid might lead to dangerous symptoms, it is advisable to use the Kroenig instrument (Fig. 19). The calibre of the measuring tube is so small that a few drops of fluid are sufficient to fill it. If the column of fluid does not show any oscillation, it is an indication that there is compression of the structures at the base of the brain, and further withdrawal of fluid must be discontinued.

Crohn has devised a useful apparatus which permits of the withdrawal of a minimum amount of fluid for the registration of the pressure in the subarachnoid space. The apparatus consists of the parts shown in Fig. 20. It presents the advantages that

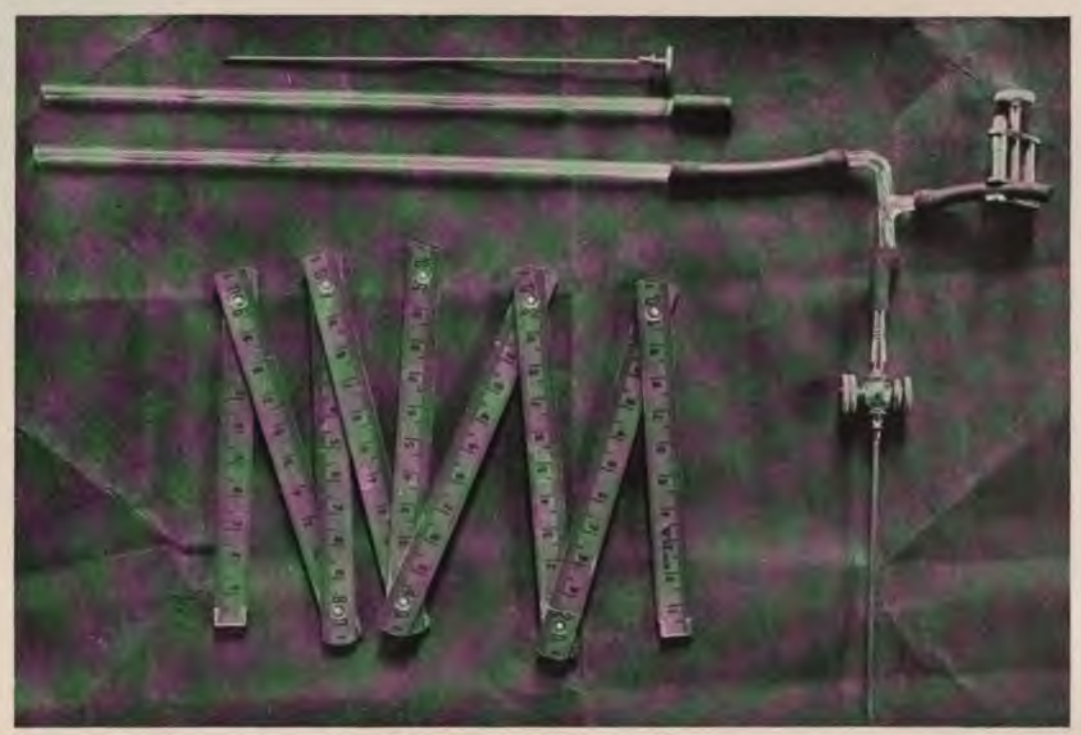

FIG. 19.—Kroenig's lumbar puncture apparatus.

there is no opportunity for the accidental escape of fluid and the registering apparatus is small and graduated.

Preparation and Position of the Patient and Operator.—We almost invariably puncture in the horizontal position. In the event of an apparently dry tap, it may very occasionally be desirable to increase the pressure of the cerebrospinal fluid by placing the patient in the sitting posture. It has been claimed that in this posture sedimentation of cerebrospinal exudate occurs, thus facilitating the search for abnormal elements. This advantage is largely a theoretical one, and is more than counterbalanced by the added danger of collapse during the performance of the puncture and the greater difficulty in technic encountered when puncture is done in a sitting posture. The patient is placed on the left

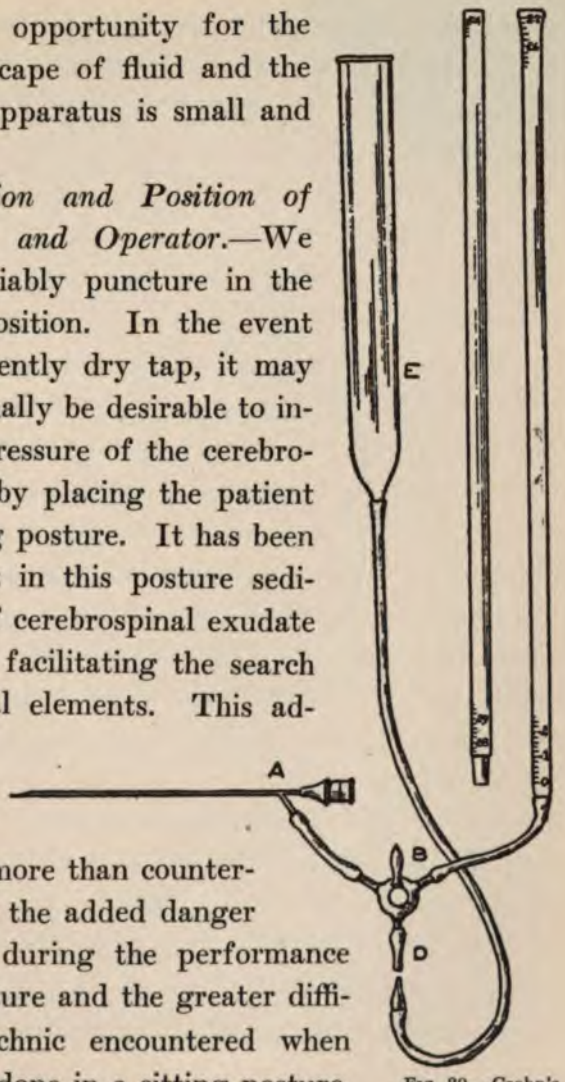

FIG. 20.—Crohn's apparatus for estimation of pressure in the cerebrospinal system.

side close to the edge of the operating table or bed. One assistant faces the patient and flexes the spine by grasping with his right hand the nape of the neck and with his left hand the legs. This position prevents struggling of the patient, brings into prominence the lumbar spines, and increases the elastic pressure of the spinal fluid. A second assistant, during the time that the operator is disinfecting his hands, renders surgically aseptic the skin at the site and vicinity of the puncture. Recently we have applied tincture of iodine on the dry skin for sterilization of the field of operation, with very satisfactory results. At the edge of the table or bed and on the floor are spread wet bichloride towels, and sterile towels are arranged about the field of operation. An anæsthetic is usually not required. The needle, manometer, tubing with the attached conus, and the measuring tape are sterilized by boiling.

Method of Procedure.—The operator locates the desired space and steadies the vertebra above by placing the thumb and middle finger of the left hand on the laminæ, and the index finger on the spinous process (Fig. 21). Grasping the needle and enclosed stilette in the right hand, and placing the index finger on the needle at the level at which it is assumed the needle will penetrate (*i.e.,* from two to five centimetres, according to the age), it is plunged in the

FIG. 21.—Position of patient with the needle introduced into the cerebrospinal canal.

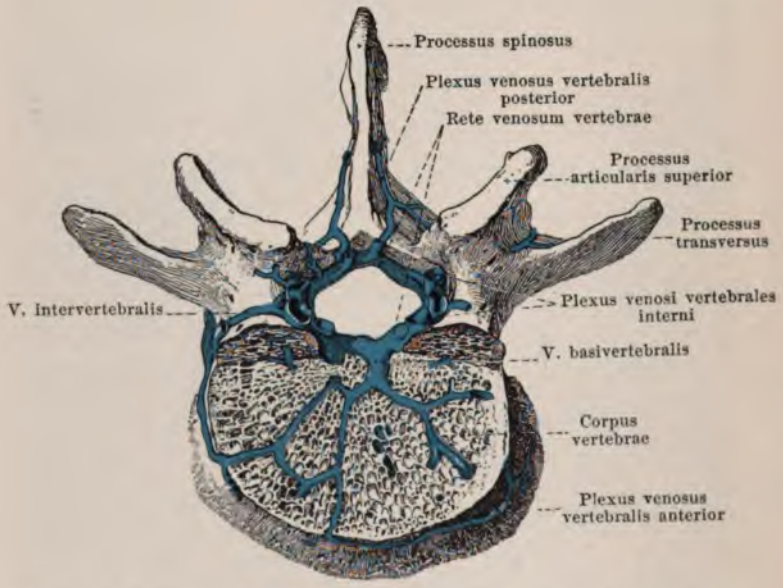

FIG. 23.—Spinal veins in a horizontal section viewed from above. Only the body of the vertebra has been cut through. (Spalteholz.)

middle line of the space and along the upper border of the lower spinous process (so as to avoid the tubercle on the posterior extremity of the inferior surface of the spinous process), in a direction almost horizontal and at an inferior (caudad) angle of 10° to the axis of the spine (Fig. 22). By directing the needle in this manner, it can be inserted to a deeper level without encountering the anterior venous plexus of the vertebral column (Fig. 23). Inexperienced operators often make the blunder of pushing the needle directly forward, and thus frequently obtain bloody fluid. This untoward result, while not usually dangerous to the patient, often renders it impossible for us to judge of the macroscopic appearance of the fluid. In the absence of the important data yielded by the gross appearance of the fluid, it may be very difficult to decide whether to inject serum at once or not. The stilette is now withdrawn and the conus at once inserted into the hilt of the needle, thus connecting the latter with the manometer by means of the rubber tubing. The horizontal

FIG. 22.—Showing direction of needle.

arm of the manometer tube is held about three centimetres below the level of the needle until the cerebrospinal fluid appears in the manometer. The horizontal arm of the instrument is then raised to the level of the needle and the height of the column of fluid in the manometer is read off on the tape, its zero mark having been placed at the level of the site of puncture (Fig. 24). The manometer is again lowered and the desired amount of fluid allowed to escape into sterile tubes. From time to time the pressure should be read by raising the tube, so as to prevent the production of a subnormal pressure in the subarachnoid space. The evacuation of the fluid should proceed slowly. The rate of flow is regulated by raising or lowering the manometer. If the flow is very slow because of low hydrostatic pressure, it may at times be artificially increased by more forcible flexion of the spine (elastic pressure) or by making the patient cough, cry, or breathe deeply, or by compressing the patient's abdomen (vascular pressure).

The use of the manometer as a routine is advisable, because the pressure constitutes the best guide in deciding how much fluid it is safe to withdraw (Figs. 25 and 26). It is probable that some of the reported fatalities have occurred as a result of too free or too rapid evacuation of the fluid. This can be avoided

FIG. 25.—Estimation of pressure of cerebrospinal fluid by means of Quincke's manometer.

FIG. 26.—Introduction of antimeningitis serum into the spinal canal, by means of funnel.

if the pressure is carefully observed at frequent intervals and never allowed to fall much below normal.

If the fluid does not appear immediately upon the

Fig. 24.—Measuring the pressure. (After Quincke.)

withdrawal of the stilette, it should not be concluded that there is a " dry tap," before waiting the reasonable period and trying the artificial means of in-

creasing pressure. If these attempts are unsuccessful, the needle should be left *in situ* and another needle inserted in the space above. A small quantity of sterile salt solution is then allowed to flow through the upper needle, and if it escapes from the lower needle we may be certain that both needles are in the subdural space. Only when this procedure has been carried out are we justified in speaking of " dry tap." This is usually due to obliteration or valvular closure of the foramina of Magendie or Luschka or the aqueduct of Sylvius. In some cases so-called " dry taps " are due to pushing forward instead of penetration of the dura by the point of the needle, picking up of nerve-roots, or occlusion of the lumen by tissue, fibrin, or pus. Such occlusion is usually readily overcome by reinserting the stilette.

It is of the greatest importance that the patient be watched, either by the operator or a competent medical assistant, for at least a period of fifteen to twenty minutes after the performance of a puncture. Occasionally sudden cessation of respiration (apnœa) takes place during this period, and, unless artificial respiration is resorted to immediately on its occurrence, a fatal result may take place.

Physiology.—The secretion of cerebrospinal fluid is chiefly effected through the agency of the various choroid plexuses. It is not unlikely that the blood-

vessels of the meninges also play a part in its production. In addition to its serving as a lubricating fluid, the cerebrospinal fluid maintains the intracranial pressure, which tends to vary with cardiac action, respiratory rhythm, and changes in the position of the body, at a constant level. The pressure in the subarachnoid space is always a few millimetres of mercury above the cerebral venous pressure. To this is due the flow of fluid from the subarachnoid space into the venous system. As the specific gravity of the blood is greater than that of the cerebrospinal fluid, the osmotic exchange is in the same direction. The intracranial pressure, as well as the pressure in the subarachnoid space in the adult and older child, is maintained at a fairly constant level through the agency of the Pacchionian bodies. With the systolic expansion of the arteries at the base of the brain, the Pacchionian bodies and the cerebral veins are compressed and emptied of the cerebrospinal fluid present in them, which flows through the thin layer of the dura into the sinuses. During the diastolic period the Pacchionian bodies expand and aspirate the cerebrospinal fluid from the subdural and subarachnoid spaces.

In infancy the functions of the rudimentary Pacchionian bodies are performed by the fontanelles,

which by their alternate expansion and retraction maintain the intracranial pressure at a normal level.

By injecting ink into the subarachnoid spaces of animals and following the movements of the particles, Sicard has been able to demonstrate the existence of a circulation in the cerebrospinal fluid. Within from two to four hours of the injection of the ink in the lumbar region, the particles had reached the occipito-atloid region. Somewhat later the base of the brain in the region between the peduncles and, still later, the lateral ventricles were reached. No ink was present in the cerebral cortex before ten to twelve hours. Injected in the occipito-atloid region the base of the brain was reached in one-half to one hour, then the lateral ventricles and lumbar region. The cerebral cortex was attained at a much later period. Injected within the cranial arachnoid, the particles of ink remained *in situ* for ten to twelve hours. He found that substances in solution in the cerebrospinal fluid were removed by osmosis, while solid particles in suspension were removed by leucocytic diapedesis.

Characteristics of Normal Cerebrospinal Fluid.— It is a perfectly clear and limpid fluid resembling spring water. The amount varies with age and sex, and does not usually exceed 60 to 80 cubic centimetres (Howell) in the normal adult. It possesses few cellular elements, usually not more than two to

seven cells per cubic millimetre. Polymorphonuclear cells are never present in normal cerebrospinal fluid. According to Peyton-Rous, the average protein content is 0.3 gram per litre, but it may vary from 1/6 to 3/8 of a gram. The normal pressure in the subarachnoid space is estimated variously by different observers. Quincke gives it at 30 to 50 millimetres of water. Krönig finds it to vary from 120 to 180 millimetres, whereas Peyton-Rous found variations from 70 to 300 millimetres. It is altered by coughing, straining, fright, and change in the position of the patient. It rarely coagulates spontaneously. It possesses no toxic properties, but in vitro it is bactericidal.

Cerebrospinal Fuid in Meningococcus Meningitis.—The fluid shows great variations according to the type and stage of the disease. The rate of flow is far from uniform. At times it flows drop by drop; at other times it runs freely in a continuous stream. There is likewise marked variation in pressure. The lowest pressure we have seen was 40 millimetres (about normal) in an infant seventeen months old; the highest 510 millimetres in a child seven years of age. In the acute stage, with proper technic it is usually possible to remove a quantity of fluid sufficient for examination. Not infrequently we have succeeded in obtaining from thirty to forty cubic

centimetres of fluid. In the chronic stage, and particularly in cases of the posterior basic type, " dry taps " are relatively frequent.

Macroscopic Appearances.—At the height of the disease the fluid is usually grayish-yellow, turbid, or purulent; at times it is so thick that it does not flow with ease through the needle. In the first twenty-four hours it is frequently clear or only slightly opalescent. On standing in the case of a purulent fluid a yellowish, homogenous and viscid deposit collects at the bottom of the tube, while the supernatant fluid becomes somewhat clarified. A fibrin reticulum is occasionally seen floating in the fluid or adherent to the tube. Along the sides of the tube a deposit of fine yellow flakes resembling sulphur particles may form. As a rule, no prognostic data are derivable from the degree of turbidity or purulence.

Microscopic Appearance.—It is usually necessary to centrifugalize the fluid. The predominant cell at this stage of the disease is the polymorphonuclear. It is usually present in the proportion of 80 to 100 per cent. of the total cell contents. It rarely gives the appearance of the normal polymorphonuclear cell of the blood. Usually its borders lack sharpness and the protoplasm is homogeneous, non-granular, and vacuolated. The chromatin network of the nucleus

is not sharply stained. At times the nucleus disappears. Some of the cells are so markedly degenerated that only a cellular débris remains. The lymphocytes are usually present in the proportion of 10 to 15 per cent. As a rule, they show less degeneration than the polymorphonuclears. In addition to these cells there are present a variable number of large mononuclear cells. They possess homogenous protoplasm and a poorly staining reniform or rounded nucleus. Frequently there are vacuoles present which contain one or more ingested cells. These large cells, as we have seen, are derived from the connective tissue and adventitia of the blood-vessels of the meninges.

In the early stages the meningococcus is present in considerable abundance in the cerebrospinal fluid. At times, even when few pus-cells are present, hundreds of micro-organisms may be seen in a microscopic field. The relative proportion of extra- and intracellular organisms varies greatly. As we shall see later, soon after the injection of anti-meningococcic serum, the greater number of extracellular organisms disappears from the fluid. It is important to remember that occasionally great difficulty is encountered in demonstrating microscopically or culturally the presence of the meningococcus, even when the fluid shows marked turbidity and the cellular elements

are present in great abundance. In these cases, as will be seen later, the precipito reaction of Vincent and Bellot may prove invaluable as a diagnostic aid. It is needless to add that the Gram stain must always be employed. Only Gram-negative diplococci having the characteristic morphology and grouping of the meningococcus are to be considered as meningococci. Where a laboratory is available, cultivation of the organism and subsequent submission to fermentation and agglutination tests are desirable.

Chemical Characters.—In addition to the more important cytological and bacteriological changes present in the acute stage of meningococcus meningitis, there are seen a number of alterations in the chemical characters of the cerebrospinal fluid. Albumin, determined either by the heat or nitric acid test, is increased in quantity, being in the proportion of 2 to 3 grams per litre. Sugar is usually decreased, but this is not a constant feature. It is often asserted that the absence of sugar from the cerebrospinal fluid is an important differential characteristic between this form of meningitis and tuberculous meningitis. This assertion is not borne out by our personal observations, for we have not infrequently seen an apparently normal quantity of sugar in the cerebrospinal fluid of meningococcus meningitis. Similar

observations on the inconstancy of this feature are recorded by Sophian. The chlorides are somewhat diminished. Cryoscopy usually shows a lowering of Δ, but there is no uniformity in the results obtained by those who have studied this physical property of the fluid. Kopetzky found a decrease in alkalinity due to the presence of combined acid. This observer was also able to demonstrate the presence of lactic acid.

Changes in the Cerebrospinal Fluid in the Course of the Disease.—According to Netter, who has made a number of important contributions on this phase of the subject, the cerebrospinal fluid in seventy-five per cent. of the cases during the first twenty hours of the disease is clear or slightly opalescent, rich in albumin and poor in cells, and contains an abundant number of meningococci. In an infant 6 weeks of age we have seen a perfectly clear fluid under slightly increased pressure, free from meningococci on the third day of the disease. Two days later, on the day preceding death, the fluid was slightly turbid and yielded a moderate number of meningococci. Too much stress can not be laid on the fact, not always clearly recognized, that the presence of clear fluid does not necessarily exclude the existence of meningococcic infection of the meninges.

With the subsidence of acute symptoms the

number of cellular elements gradually diminishes and the relative proportions of the various cells described above undergo important changes. With the diminution in the number of cells, the cerebrospinal fluid becomes less and less turbid. The polymorphonuclears and large mononuclears gradually disappear, while the relative number of lymphocytes becomes increased. At this stage of the disease the cytologic character of the fluid is not unlike that usually seen in tuberculous meningitis. Even at an advanced stage of convalescence, eight to ten days after complete disappearance of all acute symptoms, the cerebrospinal fluid may show a considerable number of lymphocytes. It has not been definitely determined when the fluid finally assumes all its normal characteristics. The disappearance of the meningococcus from the fluid is even more rapid than that of the polymorphonuclears. The free organisms usually disappear first. At the end of the first week the search for the meningococcus is quite often fruitless. Even if a few organisms are microscopically demonstrable, their viability has suffered to such a degree that cultivation on suitable artificial media is rarely crowned with success.

The orderly progression of the changes above described is, however, subject to unaccountable variations. From time to time, often in the absence of any change in the clinical symptoms, a fluid is with-

drawn differing markedly in character from the fluid obtained by the immediately preceding puncture. It may be very turbid, though previously quite clear. The number of polymorphonuclears may show a sudden marked increase. In other cases the meningococci become greatly increased in number. The explanation for these sudden changes is not quite clear. In the absence of clinical evidence of an exacerbation, they can hardly be attributed to a relighting of the infectious process. The most probable explanation is that in these cases the spinal subarachnoid space, as a result of the removal of an obstruction at some point, becomes suddenly flushed with exudate coming from the ventricles and base of the brain. It can readily be seen how important it is to follow the changes in the cerebrospinal fluid by lumbar puncture at frequent intervals, until there is definite evidence of absorption of the entire exudate.

As we shall see later, the rapidity of the regressive changes in the cerebrospinal fluid is much greater when antimeningococcic serum is introduced in the subarachnoid space. The extracellular organisms become greatly diminished or disappear entirely after the first injection. Meningococci are rarely found after the third injection. The cellular elements likewise show a rapid decrease in number and the fluid becomes clear in a much shorter time.

THE CHARACTER OF THE CEREBROSPINAL FLUID IN THE VARIOUS TYPES OF MENINGOCOCCUS MENINGITIS

Fulminating Type.—The appearance and characters of the cerebrospinal fluid in this type of meningitis are not uniform. Most commonly, on account of the rapidity of the intoxication and the lack of time for the development of severe inflammatory changes, the fluid withdrawn is clear and contains an increased amount of albumin, few cellular elements, and a variable number of organisms. The predominant cell, unlike that found in the ordinary type of meningitis, is the lymphocyte.

In some cases which are not truly fulminating in type, as a careful anamnesis reveals the presence for several days of a number of prodromal symptoms, the cerebrospinal fluid shows the usual appearance and cytological characteristics of the fluid in the ordinary acute type of this disease.

In other cases the fluid is practically sterile and normal in appearance. Without a careful microscopic examination of the meninges, it is often difficult in these cases to say whether a true meningitis is present or a fulminating form of meningococcæmia.

Mild Type.—The fluid is usually clear, albuminous, and contains a variable number of cells and organisms. In other cases the fluid is turbid and does

not differ from that present in more severe types of the disease.

Abortive Types.—In these cases the cerebrospinal fluid is usually clear and shows only slight increase in albumin and cells. The meningococcus is only rarely discoverable. In other cases the fluid shows no departure from the normal. The diagnosis must be based on the clinical course of the disease rather than the character of the cerebrospinal fluid.

Chronic Types.—At times, especially in the cases belonging to the posterior basic type, it is difficult to evacuate fluid from the spinal subarachnoid space. Several causes separately or in combination may contribute to this result. It is usually assumed that obliteration of the foramen of Magendie is the cause most frequently present. In other cases adhesions in the vicinity of the cerebellum and pons obliterate the communication between the cerebral and spinal subarachnoid spaces. In others it must be assumed that the obstruction is valvular rather than organic in nature.

The fluid is usually clear and slightly yellow or grayish in color. The few cells present are composed almost exclusively of small lymphocytes. The meningococcus is often absent, or present in such small numbers that prolonged microscopic search is re-

quired. Successful growth on artificial media is rarely attainable. In these cases intraventricular puncture may evacuate a fluid differing markedly from that yielded by lumbar puncture. Long after it has disappeared from the spinal fluid, the meningococcus may be found in the ventricular exudate.

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CHAPTER X

Complications and Sequelæ of Meningococcus Meningitis

Owing to the great variations exhibited by the clinical picture of the disease in different epidemics, it is rather difficult to draw the dividing line between those symptoms which constitute an integral part of the disease and those which may properly be called complications. The number and severity of the latter vary markedly in individual epidemics. Involvement of the eyes, ears, lungs, or joints may be seen in a considerable proportion of the cases in one epidemic and but rarely in another. Moreover, there may be great variations in the frequency of certain complications at different stages of the same epidemic. One of the most frequent and important complications, which is practically always present in the protracted forms of the disease, is hydrocephalus. On account of its importance from the stand-point of immediate and ultimate prognosis, both as regards life and the mental condition of the patient, it will receive extended treatment in another chapter. Here we shall discuss a number of complications involving the nervous system, special senses, and viscera.

NERVOUS COMPLICATIONS

These may be divided into psychic, motor, and sensory.

Psychic.—While the delirium usually seen at the height of the disease is ordinarily of a mild character, it occasionally becomes so violent that restraint by a straight-jacket is demanded. Occasionally the patients suffer for days at a time from hallucinations and delusions. In the fulminating and hyperacute types, deep coma may be present throughout the whole stormy course of the disease. In one case that made a complete recovery, a cataleptic state of several weeks' duration was observed during the height of the disease (Fig. 27).

Motor.—These have varied greatly both in frequency and severity in different epidemics. While cranial-nerve paralyses are comparatively frequent, those of the spinal nerves are rarely encountered. As we have seen, disturbances of the extrinsic muscles of the eye, manifested in various forms of strabismus and deviations, are quite frequently present at one stage or another of the disease. The opinion as to the frequency and permanence of paralysis of the extremities in this disease has undergone great changes from time to time. The observers of the early period of the clinical recognition of the disease,

FIG. 27.—Catalepsy complicating cerebrospinal meningitis, age six years.

such as Tourdes, Hirsch, Niemeyer, and Leyden, considered paralysis of the extremities a rare complication. Subsequent to this period a comparatively large number of cases showing this complication was reported in the literature. This was probably due to confusion of this disease with acute anterior poliomyelitis, in which, as we know, early symptoms of meningeal irritation are at times quite common. Since the advent of lumbar puncture, which permits the making of an accurate differential diagnosis between the two diseases, the pendulum of medical opinion has swung back to the earlier view that this complication is rare. The infrequency of paralysis of the limbs is seen from the following statistics, quoted from Netter and Debré.

Tourdes (1843) saw among 196 cases one case of preagonal hemiplegia; one hemiplegia accompanied by pain, cured; and monoplegia in a fatal case.

Niemeyer (1865) saw in 126 cases only one hemiplegia in a fatal case.

Councilman, Mallory and Wright (1898) saw in 111 cases two hemiplegias, cured; one monoplegia of the leg, cured.

Goeppert (1904) saw in 300 cases four hemiplegias; one paraplegia, cured.

Netter (before the use of serum) in 33 cases saw one hemiplegia; one spinal-root paralysis, cured.

In 100 cases (since the use of serum) he had 2 spinal-root paralyses, cured.

Hemiplegia is the most frequent form of this paralysis. It is occasionally seen in severe cases shortly before death. Usually, though the muscles show some degree of weakness and the gait is unsteady, the reflexes remain normal. The paralysis lasts from a few days to several weeks. Complete recovery is the rule. Incurable cases of hemiplegia, showing exaggeration of the deep reflexes and at the later stage muscular contractures, are extremely rare.

Flaccid paralysis of a number or of all of the muscles of one extremity is still more rare. Being radicular or neuritic in origin, pain or tenderness along the course of the affected nerve is a frequent accompaniment of this form of paralysis. As might be expected, loss of deep reflexes, change in electrical reaction (at times reaction of degeneration), and muscular atrophy are usually present. Though the paralysis may persist for months, ultimate recovery almost always results. Authentic cases of permanent flaccid paralysis, due to destruction of the motor ganglion-cells of the anterior horn, are extremely rare. Many of the cases reported in the literature probably belong to the meningeal type of anterior poliomyelitis.

CEREBROSPINAL MENINGITIS (EPIDEMIC).—M. W., age 3½ years; admitted May 13, 1911; discharged, well, June 22, 1911.

Family History.—Negative.

Past History.—Full term; normal delivery. Tonsillitis; bronchitis; diphtheria 1½ years ago; no exanthemata.

Present Illness.—May 12, after supper child was noticed to be somnolent, but did not have any definite complaint. This morning had frequent generalized convulsions, between which child was stuporous. Vomited spontaneously several times. High fever all day.

Examination.—General condition good; well nourished. Alternately irritable and talkative. Stuporous. Active delirium at times.

Eyes: React to light; weakness of right external rectus; does not seem to see.

Head: No rigidity; Macewen present; no facial.

Mouth: Tonsils much enlarged and reddened.

Extremities: During period of stupor are flaccid. Knee-jerk obtained on both sides, but diminished. No Kernig; no Babinski; no Oppenheim; no paralyses.

Skin: Few ecchymotic spots over arms and legs (traumatic?). No tache.

May 13: Lumbar puncture: 30 cubic centimetres of very turbid fluid under increased tension removed; 25 cubic centimetres antimeningococcus serum injected. Examination of Fluid: Cytology, polynuclears 100 per cent.; bacteriology, smears show intra- and extracellular Gram-negative reniform diplococcus; culture shows no growth; albumin 2 mm.; reduction 0.

May 20: On admission, patient showed signs of an acute

encephalitis and no special symptoms. Following lumbar puncture and injection of serum, temperature dropped from 104.2° F. to normal, with immediate improvement. Delirium ceased. Slight external rectus palsy on right side disappeared. No Kernig or rigidity. Patient now well and sits up in bed.

May 27: To-day noted distinct paralysis of left lower extremity: is unable to pull it up. Distinct atrophy of muscles of thigh and leg; absence of reflex.

June 10: General condition good; patient out of bed. Paralysis of leg has improved, although walk is unsteady. Knee-jerk present. Some slight weakness of left abdominal muscle.

June 22: Leg gradually improving, although it is still dragged somewhat. Discharged well.

Sensory.—Cutaneous and muscular hyperæsthesia may at times be so pronounced as to constitute a veritable complication. It may be localized or general.

OCULAR COMPLICATIONS

In the earlier literature but slight attention was paid to the visual apparatus in this disease. This is partly owing to the fact that grave and permanent lesions are but seldom present. The milder disturbances are often so fleeting in character that unless specially looked for they are likely to escape observation.

The pathogenesis of the ocular manifestations of this disease varies with the seat of the morbid process.

We may distinguish two types of symptoms: First, those referable to the various membranes and media of the eyeball and the tissues of the orbit, such as the conjunctiva, cornea, sclera, iris, choroid, and cellular tissue of the orbit. These are due either to direct propagation of the inflammatory process from the nasopharynx along the lachrymal duct or to hematogenous infection. Second, those referable to the neuromuscular system of the eye: These are due to inflammatory or toxic changes in the brain or to direct extension of the inflammatory process in the meninges along the arachnoid sheaths of the nerves of the eye. The former group of symptoms have apparently no direct connection with the morbid changes in the meninges. The eye lesions often appear simultaneously with those of the meninges. Occasionally they precede them. The symptoms of neuromuscular origin, dependent as they are upon the meningeal changes, are usually more pronounced and severe in the protracted cases.

Conjunctivitis.—Acute catarrhal conjunctivitis is quite frequent in the first few days of the disease. Shaw found it in 60 per cent. of the Belfast cases. The meningococcus is generally absent from the discharge, but it has been found by Koplik, Robinson, and others. Conjunctivitis is occasionally present at a more advanced stage of the disease. It is then

probably due to the constant exposure of the eyes present in coma.

Conjunctival Hemorrhages.—Though rarely present, they are of great aid in the differential diagnosis, as they are practically never seen in other forms of meningitis.

Keratitis.—Infiltration and steaminess of the cornea are quite frequent in cases of protracted coma. In severe cases superficial corneal ulcers may develop. They usually heal without perforation.

Iridochoroiditis (Metastatic Ophthalmia).—As we shall see later, the early occurrence of this grave but fortunately rare complication has an important bearing upon the question of the mode of infection in this disease. Though it has been seen in mild as well as in severe cases, it occurs most frequently in the malignant type and in cases of meningococcæmia in which meningitis does not develop. It is usually unilateral. Sympathetic ophthalmia of the other eye is never seen. This complication may appear at any stage of the disease, but is most frequent in the first few days. Within the last few years a noticeable diminution in the frequency of this complication has taken place. It is probably attributable to the early employment of the specific serum.

Within a few days from the onset moderate chemosis and exophthalmus set in, and the media

become slightly turbid. A purulent exudate collects in the anterior chamber; the eye becomes soft, and a yellow reflex is seen from the depth of the pupil. At a later stage the injection and swelling of the conjunctiva diminish, the cornea becomes clear; the softness of the eyeball, however, becomes more marked. The exudate in organizing drags on the retina and causes its detachment. In the final stage the bulb atrophies, the lens becomes opaque, and complete loss of vision ensues. More rarely the course of the affection is still more stormy, panophthalmia and perforation occurring within a few days.

Orbital Cellulitis.—This rare complication is probably the result of direct extension of the nasopharyngeal inflammation into the orbit along the accessory sinuses of the skull. Suppuration of the orbital tissue occasionally results.

Disturbances of the Extrinsic Ocular Muscles.—In the chapter on Symptomatology we have noted the frequent occurrence of symptoms referable to the extrinsic muscles of the eye. They are not constant, but change from day to day, and at times even during a single examination. This is due to the fact that they are spasmodic in nature and the result of cortical irritation. Persistent paralysis of the ocular muscles, seen so commonly in tuberculous meningitis,

is comparatively rare in this form of meningitis. When present, it occurs in the form of unilateral paralysis of the abducens. Paralysis of the third nerve, manifested in ptosis, divergent strabismus, or total ophthalmoplegia, is much less common. Paralyses of the extrinsic ocular muscles, when present, are seen most frequently at the height of the disease, and almost always disappear completely during convalescence.

Disturbances of the Intrinsic Ocular Muscles.—The various pupillary changes which so frequently accompany the disease have been described in the chapter on Symptomatology. They are usually so mild in character and of such brief duration that they can hardly be considered as complications.

Amaurosis.—This dreaded complication, which fortunately is somewhat rare, may be seen in all types of meningococcus meningitis. It is, however, by far most frequent in the posterior basic cases. It usually occurs at an advanced stage of the disease and is almost always bilateral. The failing vision may develop so insidiously that for a considerable time it may not be perceived by the patient. In other cases, which are less frequent, it first appears on the third or fourth day of the disease, and within a few weeks incurable blindness ensues. In other cases the amaurosis is sudden and complete, but,

after a period lasting from a few days to several months, gradual recovery takes place. In most of the chronic cases associated with hydrocephalus, there is evidence, on ophthalmoscopic examination, of more or less pronounced stasis and optic neuritis. At a later stage optic atrophy is almost always present. In cases of sudden amaurosis there are at times no abnormal changes in the fundus. It is assumed that the blindness in these cases is due to transitory œdema of the visual centres in the cortex.

AURAL COMPLICATIONS

Otitis Media.—Acute catarrhal otitis media is an early and frequent complication of meningococcus meningitis. Goeppert found it in 35 per cent. of his cases during the first week and in 75 per cent. during the second and third weeks. It so rarely gives rise to subjective symptoms that its presence is likely to be overlooked unless the ears are examined at frequent intervals. Spontaneous perforation of the drum membrane is very rare. In some cases suppuration of the middle ear occurs. Involvement of the mastoid cells is extremely rare.

Deafness.—This is one of the most frequent of the serious complications of meningococcus meningitis. It is most often seen in the severe cases, but

its occurrence has been reported in mild and even abortive cases. There are recorded in the literature epidemics of meningitis in which a large proportion of the patients developed this complication. Some of these epidemics were of an extremely mild type. It is almost always bilateral and is seen most frequently at an early period of the disease. This complication is especially to be dreaded in childhood, as in children below seven to eight years of age it almost always leads to associated mutism. How frequently this disease plays a rôle in the production of deaf-mutism is shown in the following statistics, taken from Gassot's thesis:

Castex attributes 40 cases among 178 acquired deaf-mutes to meningococcus meningitis.

St. Hilaire attributes 44 cases among 90 acquired deaf-mutes to meningococcus meningitis.

Bezold attributes 6 cases among 70 acquired deaf-mutes to meningococcus meningitis.

Kichhefel attributes 4 cases among 15 acquired deaf-mutes to meningococcus meningitis.

Denker attributes 16 cases among 32 acquired deaf-mutes to meningococcus meningitis.

Haberman attributes 100 cases among 1137 acquired deaf-mutes to meningococcus meningitis.

Love attributes 13 cases among 80 acquired deaf-mutes to meningococcus meningitis.

Pathologic Anatomy and Pathogenesis.—During the acute stage the purulent exudate extends along the trunk of the auditory nerve into the internal auditory canal, where the auditory and facial nerves are found embedded in pus. The purulent infiltration spreads to the modiolus, utricle and saccule, and along the ramifications of the vestibular nerve. At a more advanced stage of the inflammatory process the vestibule is filled with pus and the delicate organs of audition and equilibrium suffer destruction. The exudate may break through the fenestra ovale into the middle ear. In rare cases parts of the cochlea and the organ of Corti remain unaffected, permitting the perception of a certain number of tones.

As a result of the organization of the exudate, the cavities of the internal ear, the fenestræ ovale and rotunda, and the internal auditory canal become filled up with proliferating cicatricial and osteoid tissue. The trunk and terminal filaments of the auditory nerve degenerate and become atrophied.

A number of theories have been advanced in explanation of the mode by which infection of the internal ear takes place. The early theory of Boucheron, that it is due to spread of the inflammation from the middle ear, is untenable. We have seen how mild the middle-ear inflammation is and how rarely it leads to spontaneous perforation of the tympanic

membrane. Moos attributes the infection of the internal ear to thrombosis of the arteries of the auditory nerve, which is derived from the middle meningeal artery. As the arterial supply of the facial nerve comes from another source (stylomastoid artery), this would explain the rarity of serious lesions of the facial nerve. The view generally accepted now, however, is that the inflammatory process spreads by contiguity along the arachnoid sheath of the auditory nerve. The question as to the primary localization of the infection in the internal ear has not yet been satisfactorily answered. Some writers assume the spread of the inflammation along the aqueduct of the cochlea and subsequent infection of the perilymph; others its spread into the vestibule along the terminal filaments of the auditory nerve. The relative escape of the facial nerve is attributed to the fact that the trunk of this nerve forms a compact bundle which does not permit the penetration of the purulent exudate among its fibres.

Clinical Course.—The deafness usually appears suddenly in the first few days of the disease; rarely later than the first week. It is almost always bilateral, complete, and permanent. In a very small number of cases which are due to temporary œdema of the labyrinth, the deafness is only temporary. There may not be complete loss of sound perception. In a

few cases only a certain number of notes are inaudible. Bone conduction suffers equally with air conduction. Children below seven to eight years become deaf-mutes. Even if this complication sets in after speech has begun, it ultimately leads to its disappearance. Speech is at first monotonous, then incomprehensible, and finally lost. Between the ages of eight and fifteen years, the verbal function is preserved but is altered and diminished. Preservation of audibility of some notes, even if only slight, plays an important rôle in the success of subsequent instruction.

VISCERAL COMPLICATIONS

The visceral complications of meningococcus meningitis are comparatively rare. The meningococcus has a selective action only on the meninges. It is probable that only when present in large numbers in the blood do metastatic foci in the viscera occur. But, though greater success has attended the recent efforts at its discovery in the blood, the number of organisms present in this tissue has been very small. It is therefore not surprising that visceral lesions due to the immediate presence of the meningococcus are rare. From a perusal of the literature we might gain the erroneous impression that the meningococcus is quite frequently found in tissues

other than the meninges and mucous membrane of the respiratory tract. This is, however, due to the relative preponderance of complications and unusual features among the cases considered worthy of being permanently recorded.

Arthropathy.—Epidemics show marked variations as regards the frequency of the incidence of this complication. The recent epidemic in New York was notable for the small number of cases in which there was involvement of the joints. The affection of the joints may show all grades of severity. Usually the symptoms are very mild and transitory. Occasionally mild pain is the only manifestation of the arthropathy. In other cases there are, in addition to the pain, local tenderness, swelling, redness, and moderate effusion into the joint. These symptoms usually disappear in a few days. In other much less frequent cases there are marked redness, local heat, periarticular œdema, and severe pain. In these suppuration occasionally takes place. Even when this occurs, healing usually takes place readily without the production of permanent rigidity or ankylosis. A number of joints may become involved simultaneously or in succession. Unlike gonorrhœal arthritis, the periarticular structures, such as the bursæ and tendons, are rarely involved.

Respiratory.—These complications were fre-

quently seen in the earlier epidemics of Europe and the United States. In the more recent epidemics they have been less often observed. Bronchitis may be seen early in the disease. At times it has preceded the onset of the meningeal symptoms. Pneumonic attacks, both lobar and lobular, are seen occasionally. In some cases they are undoubtedly due to aspiration of the vomitus during coma. Jacobitz has described an epidemic in which pneumonia due to the meningococcus was present in all the cases. In some meningococcus pneumonia was present without any evidence of meningitis. The pneumonic lesions at times show the simultaneous presence of both the pneumococcus and meningococcus.

Positive Blood Culture. Lobar Pneumonia as Complication.—M. K., age 14 years; admitted August 19, 1906; died September 23, 1906.

Family and Past History.—Negative.

Present History.—Has not felt quite well for past three weeks. Had some cough (no expectoration) and occasional headache. One week ago vomited and complained of headache and vertigo, but was better next day. On day of admission, feels feverish and chilly and has vomited and complains of some headache. Has rash on body.

Examination (August 20).—On admission (August 19) mind was clear and patient responded quickly to questions. To-day patient is apathetic, can be roused only with the

greatest difficulty. Cries out frequently during examination; complains of severe pain in head.

Neck shows slight rigidity.

Eyes: No palsies. Pupils negative. Conjunctivæ slightly congested; small hemorrhage in left ocular conjunctiva.

Skin: Profuse petechial rash over abdomen, chest, and arms. Lesions vary from pin-point to pin-head in size; some are fading.

Lungs: Negative. Respirations irregular in depth and frequency.

Heart: Action irregular in force and frequency. Blowing systolic murmur at apex, not transmitted. First sound reduplicated. Systolic murmur at pulmonic region over vessels of neck.

Extremities: Negative. No Kernig or Babinski.

Clinical Notes.—August 21: Case admitted as typhoid suspect; Widal reaction negative. Blood culture positive for meningococci (Dr. Libman). Lumbar puncture: 30 c.c. cloudy fluid obtained under pressure; meningococci present. During preceding twenty-four hours patient rapidly becoming worse. Can no longer be roused. Stuporous most of the time. Frequently cries out at top of voice; sometimes sings. Rigidity of neck marked. Twitchings of muscles of face, more marked on left side. Twitching of fingers. Tache cérébrale pronounced. Kernig is now marked. (Symptoms much relieved after lumbar puncture.) Eight blood counts on successive days (August 19 to 29) show leucocytosis varying between 16,000 and 40,000 with polynuclears from 76 per cent. to 90 per cent. Red cells normal.

August 22: Blood culture positive for meningococci (Dr. Libman).

August 31: Condition not materially changed since lumbar puncture. Temperature irregular and high (102° to 104.5° F.). Pulse slow and of good quality. Patient eats well; appetite good. Sleeps well, as a rule; requires hypnotic only occasionally.

September 3 to September 18: Six blood counts on different days show leucocytosis varying between 17,000 and 25,000 with 80 per cent. to 90 per cent. polynuclears.

September 6: During past week general condition has slowly become worse. Temperature remains between 102° and 104° F. Pulse more rapid and of poor quality. Patient takes nourishment poorly and is slowly emaciating. Meningeal signs unchanged. Mental condition slowly becoming clouded. Severe general bronchitis.

September 10: Temperature, which for a few days had been running a lower course, suddenly rose and continued high (104° F.). General condition much poorer. Pulse more rapid and feeble, up to 140. Meningeal signs unchanged. Extremely apathetic; takes very little nourishment. Has developed consolidation of whole of left lung.

September 12: Lumbar puncture: 14 cubic centimetres of brownish fluid obtained under low pressure. Mental condition somewhat improved.

September 15: General condition the same. Emaciation continues. Signs of consolidation still present. Temperature lower, between 101° and 103° F. Pulse somewhat slower and of slightly better quality. Respirations somewhat slower and less labored. No cyanosis.

September 19: Lumbar puncture: 35 cubic centimetres of cloudy straw-colored fluid obtained under some pressure. Report: Meningococci present, no pneumococci.

September 22: Leucocytes 28,000; polynuclears 92 per cent.

September 23: General condition gradually became poorer. Temperature came down. Signs of consolidation still present, but resolving. Signs of meningitis remained marked to the end. Died.

Pleurisy, with effusion of serum, pus, or blood, when present, is always associated with pneumonia. It is often not recognized during life.

Cardiac.—Complications referable to the heart are relatively rare in this disease. In a small number of cases meningococci have been found in the vegetations. Most of the other complications, such as pericarditis and myocarditis, are usually first discovered at autopsy.

Digestive.—Vomiting is occasionally a very persistent symptom. When frequent it is usually of grave omen. Diarrhœa is seen quite frequently in infants and young children. This is not surprising when the multiplicity of the lesions in the gastro-intestinal tract is considered.

Liver.—Slight icterus is occasionally seen. Its appearance on the first day is considered by Goeppert to be a sign of sepsis.

Genito-urinary Tract.—The rare occurrence of hemorrhagic nephritis has been reported in the literature. Multiple abscesses of the kidney are occasionally seen. Meningococci have been demonstrated in these foci by Ghon and Weichselbaum. Meningococcus pyelitis has never been encountered by us. Suppurative cystitis is occasionally observed in infants. In a case of suppurative epididymitis and vesiculitis, Pick has been able to find the meningococcus. Incontinence of urine, not infrequently associated with retention, is often present. We must guard against overlooking this important complication.

Skin.—Furunculosis has at times been seen. In chronic cases bed-sores over the sacrum, occiput, and heels are not infrequent.

SEQUELÆ OF MENINGOCOCCUS MENINGITIS

Psychic disturbances, as might well be expected, represent the most frequent sequelæ of this disease. We have seen that the paralyses occurring in this disease are usually of a transitory character. The sensory disturbances, such as deafness and blindness, though usually permanent, can not be considered as sequelæ, since most often they make their appearance before convalescence has begun. The psychic disturbances, however, usually first become manifest

after the acute disease has run its course. They are more frequent in the young. Hereditary neuropathic tendencies seem to play an important rôle in their causation. Most frequently they are due to irritation of the cortical cells, more rarely to hemorrhages or foci of softening in the brain. The frequency of these complications is shown in the following:

Voisin and Paisseau in 60 per cent. of their cases.
Netter in 20 per cent. of his cases.
Therod in 50 per cent. of his cases.
Clos in 40 per cent. of his cases.

Infants and young children frequently exhibit marked change in character. They become violent, tyrannical, brutal, and very irritable. At times they exhibit sudden paroxysms of anger. They become emotional, timid, or cowardly. They often cry or laugh without any cause; nightmare may be frequent. Some suffer from headaches, others from dizziness, and even *petit mal.* In more severe cases the appearance of speech is delayed, the face is stupid, the memory feeble, and there is lack of concentration. In adults there may be apathy, intellectual torpor, and mental confusion. Some are retiring, while others show immense egotism. Loss of memory is very frequently observed. Others suffer from lack

of concentration. In some the function of ideation is affected. Double personality is occasionally exhibited. The following table, from Goeppert, shows the frequency and duration of the psychic sequelæ in this disease. The data of Goeppert were obtained at the time the patients were discharged from the hospital, those of Altmann and Cohn after six months and two years.

	Goeppert.	Altmann.	Cohn.
Survived	175=26.5%	42	23
Entirely well	125=77%	23=55%	
Psychic disturbances	5= 4.5%	6=14%	3=13%
Weakness of memory	.....	3= 7%	3=13%
Imbecility	4= 2.75%	3= 7%	
Sudden paroxysms of anger.	.....	3= 7%	
Headache	.....	.....	over 4

The prognosis of these disturbances is uncertain. In adults it is more frequently persistent. It has been estimated by Looft that 3.7 per cent. of 539 idiots were the result of meningococcus meningitis. Netter attributes a considerable number of these cases to insufficient serotherapy.

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CHAPTER XI

Internal Hydrocephalus

By the term internal hydrocephalus we understand the abnormal accumulation of cerebrospinal fluid or exudate in the dilated ventricles of the brain. This serious and important complication occurs frequently at one stage or another of meningococcus meningitis. Indeed it is present to a more or less marked degree in all cases running a subacute or chronic course. The symptoms ascribable to this change in the condition of the brain were first described by Foerster in 1883 and further elaborated by v. Ziemssen and Hesse in a classical paper on the subject.

Pathologic Anatomy and Pathogenesis.—Dilatation of the cisterna magna is usually seen in chronic hydrocephalus. The arachnoid membrane forming the posterior wall of this cisterna may be markedly thickened. In some cases the foramen of Magendie is obliterated as a result of adhesion between the cerebellum and medulla. Where this has taken place, the cisterna magna is only slightly developed. The foramina of Luschka (the lateral outlets of the fourth ventricle) are usually dilated. Closure of these fora-

mina rarely takes place, on account of their being protected by the cerebellar peduncles. It can only occur when the arachnoid becomes greatly thickened.

According to Goeppert, cases of hydrocephalus can be grouped anatomically under three headings:

1. Cases in which there is complete obliteration of the three outlets of the fourth ventricle.

2. Cases in which the foramen of Magendie is obliterated while the foramina of Luschka show compensatory dilatation.

3. Cases in which there is no organic impediment to the flow of cerebrospinal fluid from the fourth ventricle into the subarachnoid space. To this anatomical type belong most of the cases of hydrocephalus.

In these cases and in those belonging to the second group, in which there is compensatory dilatation of the lateral foramina of Luschka, three possible factors may enter in the production of the distention of the ventricles,—namely:

1. Increase in pressure throughout the whole ventricular subarachnoid space.

2. Local increase in intraventricular pressure as a result of valvular compression, which prevents the flow of cerebrospinal fluid from the ventricles into the subarachnoid space.

3. Lack of mechanical resistance on the part of the ventricular walls, which permits their distention even under moderate intraventricular pressure.

The first factor probably plays an important rôle in the production of acute hydrocephalus occasionally seen at the onset of the disease. The intense inflammatory process leads to a rapid production of cerebrospinal fluid which the channels of excretion are unable to cope with. The ventricles, being surrounded by soft brain tissue, yield readily to the increased pressure, and acute distention results. The studies of Hohn, Levy, and Flexner on the ready absorbability of the antimeningococcic serum show that there is probably no marked interference with the absorptive functions of the subarachnoid space.

Aside from the cases in which there is anatomical obliteration of the foramina, there are others in which there is present a functional impediment to the flow of cerebrospinal fluid from the brain into the cord. Though there is a marked difference in the pressure of the fluid in the ventricles and spinal subarachnoid space during life and an increase in the pressure in the spine on sitting up the patient, at post-mortem examination there is found a ready communication between the spaces in the brain and cord. It is probable that the outlets of the fourth ventricle are temporarily obliterated by the weight of the dilated

lower horns pressing the cerebellum down against the medulla.

Occasionally cases of hydrocephalus are seen in which there is at no time a marked increase in intraventricular pressure. In a number of such cases, we have been able to prove ready communicability between the ventricular system and the spinal subarachnoid space by the injection of methylene blue in the lateral ventricles. Within fifteen to twenty minutes, the cerebrospinal fluid obtained by lumbar puncture was colored by the dye. It must be assumed that the walls of the ventricles in these cases have lost their tone and have been unable to resist even a moderate increase in pressure without becoming stretched. It is not unlikely that the presence of cachexia tends to produce this change in the condition of the walls of the ventricles.

Clinical Course.—In a most admirable paper on the subject, Koplik describes three conditions under which hydrocephalus may occur as a complication of meningococcus meningitis.

1. Acute hydrocephalus at the onset of the disease.

2. Hydrocephalus complicating meningococcus meningitis at any period after the first week.

3. Hydrocephalus in posterior basic meningitis.

The importance of the early recognition of the

appearance of hydrocephalus at the onset of the disease can not be too forcibly emphasized. The life of the patient may depend upon the rapidity with which a correct interpretation of the symptoms is made and relief of the dangerous condition by lumbar puncture is instituted. The condition appears suddenly and usually within twenty-four hours from the onset of the disease, with fever, vomiting, and headache. The patient suddenly becomes pale or ashen, the surface of the body cool, the extremities cyanotic the pupils dilated, the pulse rapid and feeble, the respirations labored and sighing, and unconsciousness rapidly sets in. In other cases the onset of the hydrocephalus seems to coincide with the onset of the disease. Stupor develops early and is rapidly followed by coma and prostration. In very severe cases the patients are limp, and the symptoms characteristic of meningitis—such as hyperæsthesia or rigidity of the neck, Kernig sign, and opisthotonus—are absent. This renders the diagnosis all the more difficult, and to establish it we must look very carefully for a tense and bulging fontanelle in young infants or the Macewen sign in older children.

Acute Hydrocephalus.—P. S., age 7 years; admitted April 18, 1906; died April 20, 1906.

Family and Past History: Negative.

Present History.—Sudden onset thirty-six hours ago with severe headache and fever. Twenty-four hours ago was unconsciousness, eyes were crossed (had not been before). Chill about twenty hours ago, followed by a convulsion lasting about fifteen minutes. Has vomited several times since, not projectile. There were restlessness and twitching of the muscles. Swallowing became very difficult. Fever continued very high. Has involuntary urination and defecation.

Examination.—General condition poor. Child comatose. Pupils negative. Presence of palsies could not be determined. Head retracted; neck rigid. No tache. Heart action somewhat irregular but of good force. Very slight Kernig. No Babinski.

Clinical Notes.—April 18: Two lumbar punctures. Turbid fluid obtained both times under very great pressure. Meningococci found in spreads and cultures. Leucocytes 26,000.

April 19: Regurgitates feedings through nose.

April 20: Child isolated because of presence of Klebs-Loeffler bacilli in nose discharge. Activity stimulated and intravenous and subcutaneous saline infusions given. Temperature kept on rising (to 104.2° F.). Child died.

The second form of hydrocephalus may occur at any period of the disease after the first week. Often it appears after most of the acute symptoms have subsided or become much ameliorated. It may have a sudden or insidious onset. In the former type the temperature rises, vomiting occurs, the headache

becomes once more very intense, the pupils dilated, the hyperæsthesia and rigidity become aggravated, the mind becomes clouded, and sopor develops. In the cases with insidious course the principal symptoms are emaciation, clouding of the intellect, paroxysms of vomiting, headache, rise of temperature, paresis of the facial muscles, strabismus, and volitional tremors.

Progressive emaciation is a striking symptom which ultimately becomes extreme despite the ingestion of large quantities of food. It differs from that seen in the course of any other acute disease and seems to be trophic in nature. The skin becomes dry and scaly. A change in the mental condition is one of the earliest indications of the development of a hydrocephalus. The children show progressive loss of interest in their surroundings. They lie perfectly quiet for hours at a time, with eyes wide open and a peculiar vacant stare. Questions are answered in the fewest possible words. They may bite their nails or scratch their nose and skin almost continuously. Food is devoured greedily. Although the mind is apparently clear, the intelligence even of older patients is no greater than that of a baby six months of age. Other patients are very excitable and cry continuously. Some suffer from paroxysms

of great anxiety; others have delirium or hallucinations. In a small number of cases there is persistent unconsciousness, interrupted by convulsions which appear early in the course of the hydrocephalus.

From time to time attacks of vomiting occur. These are independent of the ingestion of food. At a more advanced stage pareses of the muscles of the face, eyes, and extremities make their appearance. There are seen intention tremors of the face, jaws, and extremities. The pupils are widely dilated. The eyes are turned downward, exposing the upper sclera. The pulse is irregular in rhythm and force. The temperature may be normal, subnormal, or intermittently elevated. The reflexes may be absent or exaggerated. Ankle-clonus, on one or both sides, is present in some of the cases. The Babinski reflex may be present from time to time. In practically all the children in which the fontanelles are closed, one of the earliest indications of the presence of hydrocephalus is a positive Macewen sign.

Hydrocephalus is a regular feature of the cases belonging to the posterior basic type. Why this should be the case becomes apparent when we consider the tender age of most of the patients and the fact that the lesions are chiefly localized at the posterior part of the base of the brain. In infancy

the soft brain tissue and the skullcap with its open fontanelle and loosely united sutures offer no great resistance to the accumulation of fluid in the ventricles. To this there is added a mechanical factor in the form of obliteration of the outlets of the fourth ventricle by the inflammatory exudate at the base of the brain.

It is very difficult to separate the symptoms referable to the hydrocephalus from those which are due to the meningitis proper. Percussion of the skull does not yield the Macewen sign in infants whose fontanelles are still open. Instead we get the impression of a sac with fluctuating contents.

Lumbar puncture yields varying results. In those cases in which the hydrocephalus develops at the initial stage of the disease, a considerable quantity of fluid under high pressure is usually obtainable. Where there is mechanical obstruction at the base only 10 or 15 cubic centimetres of fluid under little or no pressure may be obtained. In these cases the pressure does not become higher when the patient is placed in the sitting posture or is made to cry or breathe deeply. In some cases belonging to this type only a few drops of fluid can be withdrawn. We have previously spoken of the difficulties encountered in the demonstration of the meningococcus in the cerebrospinal fluid of patients who have reached the

chronic subacute stage of the disease. To establish the diagnosis in these cases the history and clinical features must be studied with unusual care.

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CHAPTER XII

Diagnosis

Since the introduction of specific serotherapy the importance of arriving at a correct diagnosis at the earliest possible moment has become greatly enhanced. On its early establishment is dependent in large part the success of this mode of treatment. The diagnosis of the disease is readily made in some cases. It encounters insuperable difficulties in other cases. It must be based upon the history and clinical features of the disease and upon the results of the laboratory examination of the cerebrospinal fluid, blood, and the nasopharyngeal secretion. Though the examination of the cerebrospinal fluid often yields results which clinch the diagnosis, the importance of a careful clinical study of each case must not on that account be minimized. In the first place, in order to obtain cerebrospinal fluid for examination, definite indications for the performance of lumbar puncture must be present. These necessarily are derived from a careful study of the clinical features present in the individual case. Moreover, we have seen that occasionally the results of the macroscopic, chemical, cytological, and bacteriological study of the cerebro-

spinal fluid yield uncertain data, and we are thrown back upon the interpretation of the clinical features for the establishment of the diagnosis.

In this disease we usually arrive at a final diagnosis by two stages: First, we determine the probable existence of a meningitis; second, we determine that the meningitis is due to the meningococcus. As soon as a tentative diagnosis of meningitis has been made, it becomes our duty to perform a lumbar puncture and withdraw fluid for examination. The statistics to be cited later, showing to what an extent the success of serotherapy is dependent upon the early administration of the serum, demand that we arrive at a diagnosis without undue delay.

The clinical features of the disease usually enable us to make the diagnosis of meningitis. Occasionally the clinical picture permits us to make not only a definite diagnosis of meningitis but also a probable one of meningococcus meningitis.

Symptoms that speak for the presence of meningitis pure and simple are: Fever, rapid pulse and respirations, headache, vomiting, convulsions, delirium or unconsciousness, restlessness, pupillary changes, mydriasis on flexion of the head or irritation of the skin, strabismus, facial paresis, hyperæsthesia, rigidity of the neck and spine, retraction of the head, orthotonus or opisthotonus, tache cérébrale,

bulging fontanelle or Macewen sign, Kernig sign, Brudzinski neck and leg signs.

The most important of these are hyperæsthesia, bulging fontanelle in infancy or Macewen sign in older children and adults, mydriasis on attempted flexion of the head or irritation of the skin, rigidity of the neck, retraction of the head, Kernig sign, and Brudzinski's signs.

The additional features which render it probable that the meningitis is meningococcic in nature are the presence of an epidemic outbreak in the locality in which the patient resides, the sudden onset together with the absence of evidence of primary disease elsewhere, the presence of herpes, petechiæ, evanescent erythematous eruptions, and arthropathy. Moreover, the fact should constantly be borne in mind that with the exception of tuberculous meningitis, which is commonly readily distinguishable from this form of meningitis, by far the largest proportion of cases of primary meningitis belong to the meningococcic variety. So that once the diagnosis of acute primary meningitis is made, it becomes *ipso facto* probable that the disease is meningococcus meningitis.

Sources of Diagnostic Error.—Failure to make a correct diagnosis of the disease is chiefly attributable to two facts: (1) Absence of one or more of the characteristic symptoms of the disease: (2) prominence

of one or more symptoms that are more characteristic of some other disease. In cases belonging to the first class, we are misled by the non-appearance of one or more of the following symptoms: fever, psychic disturbances, rigidity of the neck and Kernig sign.

Cases are described in the literature in which the temperature was normal during the first few days of the disease. Indeed in the older descriptions of the disease, before clinical thermometry came into general use, there is frequent mention of the fact that fever was quite often absent. In the subacute and chronic cases prolonged periods of apyrexia are quite commonly seen.

Psychic disturbances are at times so slight that they are easily overlooked. The patients are apparently rational and answer questions quite intelligently. This is the more striking when we consider the gravity of the condition and the marked lesions which may be present in the meninges, brain, and cord.

A more serious source of error is absence of the characeristic rigidity of the neck. We instinctively expect this symptom to be marked in all cases, and when we fail to detect it we are likely to be thrown off our guard and thus overlook a number of other symptoms which might lead us to a correct diagnosis. Rigidity of the neck is not infrequently absent, or at

least undetected in the very young and very old patients. It is rarely present in the fulminating types of the disease and in the cases that develop acute hydrocephalus at the onset.

The Kernig sign is less frequently missed, yet cases are reported in which this sign was present at no period of the disease. It is usually in the fulminating cases with intense prostration and general relaxation that the Kernig sign is not demonstrable.

In general, we may guard against failure to make a diagnosis in these cases by bearing in mind the fact that at times some of the characteristic symptoms may not be manifest.

On the other hand, the prominence of certain symptoms may lead us to assume the existence of a wholly different disease, unless a careful and thorough examination is made. The intermittent temperature has not so rarely led to confusion of this disease with malarial fever. The paroxysms in tertian malaria, however, recur at more regular intervals and they are usually of shorter duration. The various cutaneous eruptions may give rise to diagnostic error. They may lead to the assumption that simple purpura, erythema nodosum, scarlet fever, or measles is present. The diagnosis of septicæmia may be based upon the presence of a petechial eruption, if sufficient attention is not paid to the characteristic rigidity.

Gastro-enteritis may be suspected when vomiting and diarrhœa are pronounced symptoms. Pain in the joints may mislead us into the diagnosis of rheumatic fever, while pain on lateral movements of the head may be attributed to a harmless torticollis. We can only avoid the diagnostic errors in this class of cases by a careful and thorough physical examination of each individual case and by carefully considering the clinical picture as a whole.

CHAPTER XIII

Differential Diagnosis

There are a number of infectious diseases which at times closely simulate meningitis. The most important of these are pneumonia, septicopyæmia, typhoid, typhus, influenza, tetanus, and acute anterior poliomyelitis.

Pneumonia and meningococcus meningitis have not infrequently been taken one for the other. The sudden onset, with high temperature, chill, vomiting, is seen in both diseases. Moreover, in both the early appearance of herpes is a frequent symptom. Delirium, restlessness, and labored breathing may be present in both diseases. The marked similarity between the two affections demands careful and repeated examination of the lungs. The upper parts of the axilla and the interscapular region often show the earliest signs of consolidation. The fact, however, must not be lost sight of, that occasionally pneumonia is an early complication of this form of meningitis. Needless to say that if the slightest suspicion of the existence of meningitis is entertained, lumbar puncture must be performed without undue delay.

Typhoid Fever.—The insidious onset of this disease is an important differential point from menin-

gococcus meningitis. Occasionally, however, when occurring in military epidemics, typhoid may begin with violent symptoms. Features which may be common to both diseases are epistaxis, headache, restlessness, insomnia, delirium, torpor, diarrhœa, and a roseolar eruption. In meningitis, however, the headache is more intense. Vomiting is rare in typhoid, while diarrhœa and abdominal distention are very unusual in meningitis. In the latter disease the fever has an irregular curve, the pulse is not markedly slow, the tongue not characteristically coated, and the spleen not enlarged. The Widal and diazo reactions and the number of leucocytes are valuable differential criteria.

Typhus Fever.—The similarity in the clinical picture betwen severe typhus and meningococcus meningitis is so marked that keen observers, like Murchison, have considered this form of meningitis a variety of typhus. Indeed it is very probable that in the past the two diseases were frequently confounded. Fortunately, typhus, except in a greatly attenuated form, is now rarely seen in this country. Sudden onset is common to both. Other common symptoms are purpura, delirium, muscular rigidity, and prostration. The eruption in typhus is usually more gradual in development, whereas the petechiæ and purpuric rash in meningitis, when present,

usually appear within twenty-four hours from the onset. The temperature curve is more regular, and the delirium is a somewhat later manifestation in typhus fever. The diazo-reaction is commonly present in typhus.

Influenza.—The nervous type may closely resemble meningitis. The sudden onset, with coryza, headache, pain in the back, general soreness, delirium, and vomiting, is not unlike that of meningitis.

Septicopyæmia.—The intermittent or remittent temperature, the chills, the various cutaneous eruptions, such as erythema, purpura, and petechial rash, and arthropathy may be common to both diseases. The onset in septicopyæmia is, however, usually insidious, and valvular endocarditis is much more frequent. Moreover, in many cases a primary focus of infection is to be detected upon a thorough and careful examination. A blood culture not infrequently reveals the presence of the infecting organism.

In addition to the above general infectious diseases which at times simulate meningitis, there are a number of more or less localized infections involving the nervous tissue which may give rise to confusion. The most important of these are tetanus, poliomyelitis, polioencephalitis, and meningism.

Tetanus.—The spinal rigidity, opisthotonus, pain in the limbs, and fever are common features. Con-

sciousness is retained in tetanus, while in meningitis there are usually no trismus and paroxysmal contractures and pains which form the dominant symptoms of tetanus. Headache and herpes are absent in tetanus.

Poliomyelitis.—The meningeal form of acute anterior poliomyelitis at times offers the greatest difficulty to the diagnostician. Headache, vomiting, convulsions, rigidity of the neck may be present for several days before the characteristic paralyses have made their appearance. Diffuse or local pains may be felt in the muscles and hyperæsthesia may be present. Mental symptoms, however, are usually only slight or entirely absent. In cases in which the paralysis is only slightly marked, the diagnosis may remain unsettled. Meningococcus meningitis, as we have seen, occurs most frequently in the winter and spring, whereas poliomyelitis is most prevalent in summer and autumn. The paralyses in meningitis, being radicular in origin, are associated with pain and diffuse muscular atrophy and are rarely permanent. On the other hand, the paralyses in poliomyelitis are usually not painful except in the beginning. They are, as a rule, definitely localized to a group of muscles which become permanently paralyzed and atrophied.

According to Peabody and Draper, the cerebro-

spinal fluid in poliomyelitis possesses the following characteristics. It is perfectly clear, at times fine white flakes may be seen, the pressure is moderate, there is increase of fibrin; from the second to the fourth week there is usually an increase of globulin contents.

Polioencephalitis.—While this disease usually closely resembles tuberculous meningitis, there are certain types that have a symptomatology which is almost identical with that of meningococcus meningitis. Koplik has called attention to the fact that in this disease there is a short period following the onset of a high fever during which the patient continues to be about, whereas in meningitis the prostration at the onset is usually so marked that he is compelled to go to bed at once. There is also increasing sopor extending over several days. Upon lumbar puncture there is withdrawn a clear or slightly flocculent fluid containing 90 to 100 per cent. lymphocytes and no bacteria.

Meningism (*Serous Meningitis*).—Meningism is a term first employed by Dupré for a symptom complex occurring in the course of a number of acute infectious diseases. It is most frequently seen in lobar and broncho-pneumonia, typhoid, scarlet fever, diphtheria, and whooping-cough. It is at times very difficult to distinguish clinically this morbid process

from true meningitis. The detection of the existence of a primary infection is a point of great importance. The rigidity of the neck is usually moderate and not present at all times. The Kernig sign is rarely as marked as in meningitis. Mental disturbances do not form as marked a feature. The Macewen sign and the bulging of the fontanelle are not as pronounced as in meningitis. The meningeal symptoms are of short duration.

Meningeal Hemorrhage.—At times this condition is not easily distinguished from meningococcus meningitis. In meningeal hemorrhage there is rarely any fever. Indeed the temperature is at times subnormal. The pulse is often slow and of high tension. Hyperæsthesia is usually absent. Herpes, arthropathy, and cutaneous eruptions are not seen in meningeal hemorrhage. Psychic disturbances are not common. Meningeal hemorrhage is occasionally accompanied by subconjunctival ecchymoses and severe albuminuria.

In infancy we must also consider in the differential diagnosis the following common conditions,—namely, gastro-enteritis, infantile eclampsia, and tetany.

Gastro-enteritis.—Convulsions and various cerebral symptoms, as is well known, are not uncommon in the clinical picture of infantile gastro-enteritis.

Some degree of rigidity of the neck has at times been observed. The condition of the fontanelle, when the infant is perfectly quiet, is one of the most valuable diagnostic aids. Soon after the onset of a severe attack of gastro-intestinal disturbance the fontanelle becomes depressed, whereas in meningitis, even in the presence of moderate diarrhœa, it usually becomes tense and bulging. In older children the presence of Macewen and Kernig signs, as a rule, differentiates meningitis from gastro-enteritis.

Infantile Eclampsia.—At the onset of an eclamptic seizure, especially if it is the first attack, the existence of meningitis is often suspected,—this the more readily as such an attack frequently follows or is accompanied by a sudden and sharp rise in temperature. We must carefully inquire into the possible presence of an etiological factor, such as a dietetic error. Bulging of the fontanelle is usually present in eclampsia during the convulsive seizure, but disappears in the intervals.

Tetany.—In young infants the differential diagnosis is occasionally difficult. The Trousseau and Chvostek signs and the galvanic hyperexcitability are not usually present in meningitis. On the other hand, the bulging fontanelle is not a feature of tetany. In some cases final decision is only made by lumbar puncture.

DIFFERENTIAL DIAGNOSIS BETWEEN THE VARIOUS FORMS OF MENINGITIS

Having established the existence of a meningitis, it remains for the clinician to determine, if possible, that the case belongs to the meningococcic form. The differentiation between this form and tuberculous meningitis is less difficult than between the other forms of acute suppurative meningitis.

Tuberculous Meningitis.—A tuberculous family history or one of close contact with a tuberculous individual is of considerable aid in the diagnosis, but its importance should not be over-estimated. Of much greater significance is the mode of onset. The onset of tuberculous meningitis is slow and insidious. It usually begins with moderate headache, occasional vomiting, and apathy. These symptoms continue for several weeks before the more characteristic manifestations of meningeal involvement appear. The fever is moderate during the greater part of the course. Before death, sudden hyperpyrexia is very commonly seen. There is early emaciation. The abdomen is scaphoid in shape, and obstinate constipation is the rule. The patients are indifferent, listless, and stuporous. They sleep most of the time, and do not seem to be fully conscious of their surroundings. They are less disturbed by the physician's examina-

tion. Photophobia is very frequent, whereas in meningococcus meningitis true photophobia (*i.e.*, due purely to light and not to attempts at active retraction of the eyelids) is very unusual. The pulse is usually slower and more noticeably irregular. Slow, irregular, and sighing respirations appear at a more early stage of the disease. Alternate flushing and pallor of the face is more often seen. In young infants there is marked bulging of the fontanelle early in the disease. In older children the Macewen sign is usually pronounced. Transitory palsies of the cranial nerves, such as irregularity of the pupils, ocular muscles paralysis, and facial paralysis, are very frequent. Though these symptoms are also quite common in meningococcus meningitis, they are usually less pronounced. Herpes is extremely rare in the tuberculous meningitis; eruptions and joint disease are never seen. The rigidity of the neck and Kernig sign are less pronounced, while retraction of the head and opisthotonus are practically never observed. The deep reflexes are irregular. Usually exaggerated at the onset, they are, as a rule, lost at an advanced stage of the disease. The Babinski reflex occurs in a larger proportion of cases. The cutaneous reaction of v. Pirquet is at times of great value. It is often negative at an advanced stage of the disease. The presence of choroid tubercles is

pathognomonic. Unfortunately, they are present in only a small number of the cases. There is moderate leucocytosis. It is important to bear in mind that in infancy tuberculous meningitis may run an acute course, being accompanied by high fever and gastro-intestinal disturbances. In adults the disease is occasionally very atypical and the differentiation between the two diseases a matter of extreme difficulty.

Acute Suppurative Meningitides.—A great variety of organisms are capable of producing acute inflammation of the meninges. The most important of these are the pneumococcus, streptococcus, staphylococcus, influenza bacillus, typhoid bacillus, and bacillus coli. The differentiation from meningococcus meningitis is often impossible without lumbar puncture. In otitic meningitis the history of ear discharge followed by mastoid involvement is very significant. The course is more insidious but progressive. Facial and motor oculi paralyses and unilateral labyrinthine disturbances are very common. The duration of an acute meningitis is of some diagnostic importance. A case that has lasted more than a week is likely to be of meningococcic origin.

The other forms of acute meningitis are usually fatal within a week from the onset. In pneumococcus meningitis the meninges of the spinal cord and nerves are less often affected, so that rigidity of the

neck is less common and involvement of the cranial nerves and spinal-nerve roots less frequent. Holt has called attention to the fact that, on account of the occasional localization of the inflammatory process, the pneumococcus may not be demonstrable in the cerebrospinal fluid. Acute meningitis occurring as a complication of an acute infectious disease, as pneumonia, influenza, or typhoid, can usually be distinguished from meningococcus meningitis by finding evidence of the existence of the primary disease.

Aseptic Meningitis.—In disease of the cranial bones we occasionally encounter a purulent meningitis due to irritation in which the fluid is free from bacteria. It is also well to bear in mind that very occasionally the development of a sterile purulent exudate takes place after a lumbar puncture or the injection of serum in non-meningococcic cases.

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CHAPTER XIV

Laboratory Diagnosis

The Cerebrospinal Fluid.—As has been previously stated, the final establishment of the etiologic diagnosis is based upon the study of the cerebrospinal fluid in the laboratory. No matter how certain the diagnosis is otherwise, its confirmation by laboratory investigation of the fluid is practically always indispensable.

The data yielded by the examination of the cerebrospinal fluid in the normal condition and in a number of meningeal and cerebral disturbances is given in the table opposite, which is adapted from Pfaundler's article in "The Diseases of Children," by Pfaundler and Schlossmann.

The differential diagnosis between the inflammatory exudates occurring in meningitis and the fluid found in normal conditions (*i.e.*, normal as regards the meninges and central nervous system), in meningism, and various other cerebral conditions is made by estimation of the pressure of the fluid, the macroscopic appearance, the gross fibrin contents, the protein and globulin contents, the degree of reduction by potassium permanganate, the cytological and the bacteriological features.

narks the upper limit of the puncture—namely, the horizontal line joining the il inserts a sterile needle about 1 mm. wide and fitted with a stylet, horizon- f the manometer tube is attached to the needle. The pressure during quite materially reduced below normal. The wound is closed by adhesive plaster.

ional neuro- epilepsy in sms, tetany, horea).	Sinus thrombosis.	Other pathological conditions and generally suggestive symptoms.
y increased.	Often increased.	Rapid sinking of the pressure after drawing a little fluid, with occlusion of communication to the cerebral region of dissemination of the fluid; pressure zero at "punctio sicca" (dry tap).‡ Normal or low pressure with good cardiac function excludes exudative affections.
.....	Usually tinted with blood; often brownish-green.	Bloody at puncture (unchanged appearance of elements, gradual decrease of blood contents, in various portions during voiding, strong tendency to coagulation), in hemorrhagic pachymeningitis, cerebral and meningeal hemorrhages, basal fractures, in (birth) trauma (old blood discolored, corpuscles disintegrate, coagulability absent).
ange.....	Sedimentation of disintegrated blood masses (old blood) no coagulation.	
nuclear and nuclear cells.	Slightly increased lymphocytes.	A few lymphocytes are also found in cerebral scleroses, poliomyelitis, syphilitic meningitis, otitis interna, whooping-cough, etc.
.....	Often somewhat increased.	A. greater than 0.1 per cent. only in exudations or tumors. A. greater than 0.5 per cent. only in tuberculous and suppurative meningitis (aside from the cases with puncture hemorrhage).
demonstra-	Sugar demonstrable.	Absence of sugar; usually exudation.
.....	.....	Mixed infections not seldom in tuberculous and cerebrospinal meningitis. In athrepsia often intestinal bacteria.

can be avoided. The speed at which the fluid is voided is no criterion for the

phy, etc.
the quantity present.

In meningeal irritation and inflammation there is usually found an increase in the pressure of the cerebrospinal fluid. As a rule, it is more marked in the latter than in the former. The method of estimating the pressure has been discussed in a previous chapter. In inflammatory fluids there is usually some degree of turbidity or opalescence. While normal fluid has the appearance of absolutely clear water, the fluid in inflammatory conditions of the meninges, even when apparently quite clear, will usually reveal the presence of small dancing particles when a ray of light is passed through the column of fluid.

The gross fibrin content which becomes apparent upon standing is usually increased in all forms of meningitis. The normal fluid contains very little fibrin.

The estimation of the protein content is made either by the acetic acid test of Moritz (addition of a few drops of 5 per cent. acetic acid to 2 cubic centimetres of fluid) or by the nitric acid ring test. Only a trace of albumin is present in normal fluid and in the fluid in meningism. It varies considerably in the various forms of meningitis, being less abundant in tuberculous meningitis. The globulin content can be estimated by the tests of Nonne and Apelt, Noguchi, and Braun and Husler.

Nonne and Apelt's Test.—Phase I: Equal parts

of cerebrospinal fluid and a heat-saturated solution of ammonium sulphate are mixed in the cold. The reaction is considered positive if opalescence occurs within three minutes. This occurs only when there is an increase of globulin, and is seen only in pathological specimens.

Phase II: The mixture is filtered and the filtrate is then boiled after the addition of a drop of acetic acid. A precipitate indicates the presence of albumins. A positive Phase II is seen in normal fluids.

Noguchi Test.—This is a simple and delicate test: 0.1 or 0.2 cubic centimetre of cerebrospinal fluid is mixed with 0.5 cubic centimetre of 10 per cent. solution of butyric acid in normal salt solution. The mixture is then heated over a flame for a brief period. 0.1 cubic centimetre of normal sodium hydrate solution is then quickly added to the heated mixture and the whole boiled once more. A positive reaction is shown by the formation of a granular or flocculent precipitate within two hours. In normal fluid at most only a slight opalescence or turbidity occurs.

Braun and Husler Test.—This is a modification of the test of Sachs and Altmann, and is carried out as follows:

To 1 cubic centimetre of cerebrospinal fluid there is added slowly, 1 cubic centimetre at a time, n/300 HCl, the mixture being constantly shaken. When

the test is positive, a precipitate forms within one-half hour.

A quantitative albumin estimation may be made by the use of the Esbach reagent.

Mayerhofer has shown that there is a marked difference between normal and inflammatory fluid in the degree of reduction of potassium permanganate when boiled in an acid medium. In meningitis the index of reduction is high, from 2 to 8. As it usually drops after the injection of antimeningitis serum, this test may be of some value as an indication of beginning recovery.

Three methods are in use for the examination of the cells of the cerebrospinal fluid:

1. The centrifuge method, developed by Widal, Sicard, and Ravant.

2. The cell-chamber method, introduced by Laignel-Lavastina and modified by Fuchs and Rosenthal.

3. The microtome method, introduced by Alzgeimer.

As pointed out by Bybee and Lorenz, the centrifuge method is inaccurate, owing to the fact that the cells become clumped and adhere to the bottom and sides of the centrifuge tube. Moerover, it does not permit of an accurate quantitative estimation of the cells, on account of variation in the size of the drops,

as well as the area covered by each drop. The microtome method of Alzheimer is too slow and cumbersome. Bybee and Lorenz advise a modification of the Fuchs-Rosenthal cell-chamber method. They employ a red-cell counter, and a stain composed of

Methyl violet	0.1
Glacial acetic acid	2.0
Distilled water up to	50.0

For ordinary clinical purposes, however, the use of the centrifuge and Hastings or Jenner stain gives sufficiently good results.

The cytologic examination of the cerebrospinal fluid yields extremely valuable results (Fig. 28). An increase in the cellular elements is present in all forms of inflammation of the meninges. In the purulent cases there is a preponderance of polymorphonuclear cells (80 to 100 per cent.), whereas in tuberculous meningitis the lymphocytes are greatly in excess (70 to 100 per cent.). Very recently, however, we observed a case of tuberculous meningitis (proved by finding the tubercle bacillus in the cerebrospinal fluid) in which the cells were exclusively of the polymorphonuclear types. On the other hand, it is important to bear in mind that in the later stages of meningococcus meningitis and throughout the whole course of the posterior basic cases a relative lympho-

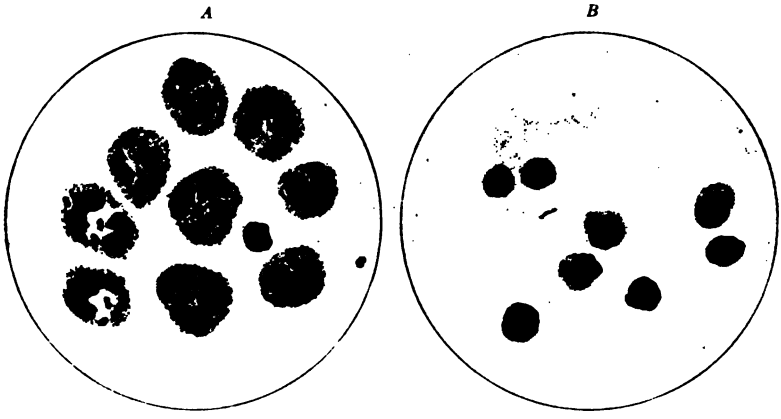

FIG. 28.—*A*, cytology of epidemic cerebrospinal meningitis. Polynuclear cells. Meningococci. *B*, cytology of tuberculous meningitis (specimen of Dr. E. P. Bernstein). Mononuclear cells. One tubercle bacillus.

cytosis is present. A diagnosis can, however, rarely be definitely based upon the cytological character of the fluid alone, without the demonstration of the organisms producing the infection.

Absolute certainty of etiologic diagnosis is attainable only by finding either microscopically or culturally the meningococcus in the cerebrospinal fluid. In the vast majority of the acute cases, we are able to do this at the first examination if we examine the fluid by the Gram stain and make cultures with sufficient quantities of fluid as soon as possible after its withdrawal.

It is desirable to make cultures in all cases, as occasionally these show the positive growth when the smears fail to reveal the presence of the meningococcus. For their microscopical identification it is, however, usually sufficient if we can demonstrate the presence in the smears of Gram-negative, intra- and extracellular, hemispherical diplococci. In chronic cases it is not at all rare to find the fluid sterile microscopically as well as culturally. In these cases the diagnosis must be based upon the history of sudden onset and the clinical picture of the disease. Differentiation from tuberculous meningitis is usually not difficult when the clinical features of the disease are carefully analyzed and the tubercle bacillus is found by long and patient search. Bernstein found tubercle

bacilli in 98 per cent. of 102 cases, while Hemenway succeeded in finding them in 135 out of 137 cases examined.

Precipito-Reaction of Vincent and Bellot.—While the cerebrospinal fluid, in contrast to the blood, does not, as a rule, possess specific agglutinins, antibodies, bacteriotropins, or opsonins in more than mere traces, Vincent and Bellot have shown that there is present in the cerebrospinal fluid of meningococcus meningitis a substance which forms a precipitate with antimeningitic serum. This is probably an extract or autolysate of the meningococcus.

The test is performed by adding from two to five drops of antimeningitis serum to fifty and one hundred drops of cerebrospinal fluid, which has been previously clarified by centrifugalization. These mixtures and a control (containing fluid but no serum) are placed in the incubator at 50° C. for eight to fourteen hours. If the fluid is one derived from a case of meningococcus meningitis, the mixtures of the fluid and serum become turbid or opalescent, while the control remains clear. The test must be performed immediately after the cerebrospinal fluid is withdrawn from the spinal canal. It must not be exposed to the air or light for any length of time. Evaporation of the fluid while in the incubator should be prevented by the use of a rubber stopper. Occa-

sionally the test first becomes positive after twenty-four to thirty-six hours' incubation. This reaction appears early in the course of the disease, within twelve hours, and persists for fifteen to twenty days. In 61 normal subjects, Vincent and Bellot found the reaction negative, while in all of 32 cases of meningococcus meningitis it was positive. Their observations were confirmed by Louis and Salebert. The test is best performed on the first lumbar puncture, as it is conceivable that the injection of serum might lead to precipitation within the canal and consequent exhaustion of the precipitable body. In some cases Letulle and Legane found that the control became spontaneously turbid, and the test was then inconclusive. In a few cases a positive reaction has been present in pneumococcus meningitis. This test may prove of great value in those cases where cerebrospinal fluid is apparently sterile. At any rate, the test is readily performed and deserves to be more generally recognized in this country.

Presence of Complement.—Weil and Kafka have demonstrated by hæmolytic tests the presence of both complement and amboceptor in the cerebrospinal fluid.

Complement Fixation.—Bruynoghe found fixation of complement by specific antigen in 12 cases of meningococcic meningitis.

Sodium Taurocholate Test.—Danielopolu found that the normal inhibition of cerebrospinal fluid on the hæmolytic action of sodium taurocholate on dog's blood is greatly increased in meningitis. He claims that this test is positive long before there is a change in the cytology of the fluid.

Animal Inoculation.—By inoculating 0.5 to 0.75 cubic centimetre of cerebrospinal fluid in the lumbar subarachnoid space of small guinea-pigs, v. Grysez produced death in from two to twenty-four hours. A reduction of temperature of 4° to 8° C. occurred within an interval varying from ten minutes to twenty-four hours. He considers the lowering of the temperature characteristic, and advises the use of this test as a valuable aid in the diagnosis of fluids that do not reveal the presence of the meningococcus.

THE BLOOD

The examination of the blood often yields results which are of great aid in the diagnosis. The presence of a well-marked polymorphonuclear leucocytosis, especially in the acute stage, serves to differentiate the disease from a number of other affections which are characterized by a normal leucocyte count or leucopænia, such as typhoid fever and anterior poliomyelitis.

Agglutination.—The agglutinative properties of

the serum in meningococcus meningitis are rather inconstant. Specific agglutinins are rarely demonstrable in the first few days of the disease. At the end of the first week the agglutination reaction is almost always positive. It disappears rapidly, and in convalescence is practically always absent. It is frequently present in the mild and abortive types, but usually not demonstrable in the chronic cases. It is naturally not to be expected in the fulminating type of the disease, as death takes place within the first forty-eight hours. It is of especial value in those cases in which the meningococcus for one reason or another cannot be found in the cerebrospinal fluid. In addition, the test may serve to clear up the nature of those cases in which the mild character of the symptoms does not justify the performance of a lumbar puncture. On account of its comparatively late appearance, a diagnosis will usually have been made before this test is employed.

Technic.—A loopful of a culture of the organism which has previously been tested as to its agglutinability is thoroughly shaken in each tube of a series containing one cubic centimetre of serum diluted in 1/10, 1/25, 1/50, 1/100, 1/200, 1/400, etc., with salt solution. These tubes, with two controls each, one of serum alone and the other of a suspension of the culture in salt solution, are then placed in the in-

cubator at 37° C. The results are read off at the end of four, eight, and twenty-four hours. A positive reaction is indicated by the formation of a visible sediment at the bottom of the tube and clarification of the supernatant fluid. The index of agglutination is the highest dilution of the serum at which such sedimentation still occurs. Kutscher has shown that at times better results are obtained if the tubes are kept in the incubator at 55° C.

Opsonic Index.—This reaction appears rather late in the disease, so that a diagnosis will usually have been made before it is employed. Houston and Rankin found a high opsonic index over four, after the sixth day of the disease. MacGregor observed the highest indices in the second and third weeks of the disease. Davis found that the index was inconstant, owing to variations in the strains of meningococci. Occasionally it persisted for two or three weeks and ran parallel with agglutinative reaction. Its absence, therefore, does not necessarily exclude the presence of meningococcus meningitis. When present, however, it makes the diagnosis almost certain, as specific opsonic action on the meningococcus is not seen in any other condition. The technic is very difficult, and if the test is to be of any value it must be carried out by one who is thoroughly versed in opsonic determinations.

Complement Fixation.—Positive results with this method have been obtained by Cohen and Schumann, but its diagnostic value is not as yet definitely determined.

Bactericidal Bodies were demonstrated in the blood by Davis and Dopter late in the disease.

Demonstration of the Meningococcus in the Blood.—A great number of investigators have found the meningococcus in the blood. The most important of these observations are those of Elser, who in a series of 41 cases succeeded in isolating the meningococcus from the blood in 11. But the number of organisms appeared to be small, as growth took place in only one or at most two of the three culture flasks used. These results indicate that in most of the cases a transient invasion of the blood stream exists and not a true septicæmia.

BACTERIOLOGICAL EXAMINATION OF THE NASOPHARYNX

We have in the previous chapter seen how constantly the meningococcus is found in the nasopharyngeal secretion of patients during the early stages of the disease, and it might therefore appear as though the bacteriological examination of this region should prove to be of considerable aid in the clinical diagnosis. Unfortunately, its practical value

is greatly limited by reason of the fact that the technic involved in the isolation of the organisms from the nasopharynx is rather long and difficult. It can only be carried out in institutions that have the proper facilities for modern bacteriological investigations.

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CHAPTER XV

Prognosis

The prognosis of meningococcus meningitis, even since the introduction of specific serotherapy, remains a comparatively grave one. In general it may be stated that the sporadic form of the disease is less severe than the epidemic form. This is well shown by the statistics of Koplik at Mount Sinai Hospital. In the five years from 1899 to 1903 inclusive, 21 sporadic cases of the disease were admitted to the Children's Service, of which 8 died,—*i.e.*, a mortality of 38 per cent. Deducting the cases below two years of age, there was left a mortality of 13 per cent. In 1904 and 1905, the two epidemic years in New York City, 74 cases were admitted, with a mortality of 50 per cent.; of these 51 cases were above two years of age, and 31 per cent. died. We thus see a striking difference in the mortality between epidemic and sporadic cases under the same form of treatment.

The mortality has varied greatly in different epidemics. Even in the same epidemic some localities exhibit a graver form of the disease than others. The severity of the disease usually diminishes toward the

end of an epidemic. In general we may state that the mortality in cases diagnosed bacteriologically and not treated by specific serum varies from 50 to 75 per cent.

Indeed, in the recent epidemics in Germany, the United States, England, and France, the mortality rate approached or even passed the upper of the two percentage rates given above. Thus, in New York City in the epidemic of 1904–1905, there were about 4000 cases with 3429 deaths,—*i.e.*, a mortality of 73.5 per cent. Chase, in Akron, Ohio, had a mortality of 90 per cent. Ladd in the same State had a mortality of 80 per cent.; while among the patients of Sladen, at Baltimore, the mortality was 64 per cent. In 1907 Robb, in Belfast, treated 275 cases, of whom 199 died,—that is, a mortality of 72.13 per cent. Of 108 patients treated by Ker, in Edinburgh, 80.5 per cent. died.

We can not attach too much importance to the statistics of the earlier authors, which is summarized by Hirsch, in his monograph, who finds the average mortality in the epidemics collated by him to be 37 per cent., on account of the lack of bacteriological proof of the nature of the disease. The reduction in mortality since the introduction of serotherapy will be statistically shown in the chapter on Treatment.

Individual Prognosis.—There are few infectious diseases in which the ultimate prognosis of any individual case is so surrounded by uncertainties as it is in meningococcus meningitis. Patients who are apparently in an extremely grave condition recover; and, on the other hand, as long as there is any fever it can not be foretold with certainty that recovery will surely take place. This is due to the fact that relapses are so common in this disease. If the pulse is over 100, even though the temperature has been normal for some time, the occurrence of a relapse is not unlikely. Similarly, as long as the Kernig sign persists, we can not be sure that the patient has escaped the danger of a relapse. According to Altman, we may confidently expect recovery if the pulse is regular and of normal frequency and the temperature has been normal for fourteen days.

Factors Influencing the Prognosis.—The previous condition of the patient plays a comparatively unimportant rôle. Patients in robust health previous to the onset of the disease may die, while delicate patients recover. Chronic alcoholism is considered by most authors a factor which seriously compromises the patient's chance of recovery.

Age.—The age of the patient is a factor of the greatest importance in the final outcome of the disease. Its influence is well shown in the following

table, in which the mortality of 211 cases treated at the Mount Sinai Hospital from 1901 to 1906 is given.

	Cured.	Unimproved.	Died.	Percentage of unimproved cases and deaths.
1 year	10	5	23	74
2 years	2	2	13	88
3–5 years	22	2	15	41
5–10 years	32	0	21	40
10–15 years	14	0	9	39
15–20 years	12	0	11	48
20–30 years	6	0	5	45
30–40 years	3	0	5	63
40–50 years	1	0	2	67
50–60 years	0	0	5	100

Early Diagnosis and Application of Serum Treatment.—By far the most important prognostic factor is the time of the first application of the serum. The tables given in the chapter on Treatment make this fact very evident. Early treatment presupposes early diagnosis. As it is a matter of considerable difficulty in infancy, this fact accounts in part for the high mortality at this period of life, even under serum treatment.

Symptoms Indicative of a Grave Condition.—The presence of one or more of the following symptoms indicates that the case in hand is of a grave nature: early and persistent coma with loss of sphincteric control; violent delirium; repeated convulsions, especially

if appearing late in the disease (in infants convulsions have not the same grave significance as in older children and adults); very rapid and small pulse; respirations above 36 in adults (this usually indicates the presence of pulmonary complications); persistent vomiting or diarrhœa; profuse purpura within the first thirty-six hours; hemorrhages from the mucous membranes; complete insomnia; general tremor; general relaxation.

The occurrence of the following complications seriously compromises the patients' chance of recovery: pneumonia; pleurisy, especially if purulent in character; pericarditis, which is usually purulent; severe hydrocephalus.

On the other hand, the following features of the disease are not of great value in the prediction of the outcome of an individual case: the character of the onset, the type and height of the temperature, the intensity of the headache, the degree of rigidity, the emaciation, the irregularity of the pulse, herpes, petechiæ, and joint involvement.

Prognosis as to Complete Recovery.—Since the early and systematic employment of the specific serum, most of the cases that recover at all regain completely their previous good health. In some cases, however, there is temporary persistence of rigidity, awkwardness in gait and movements of the arms, loss

of the tendon reflexes, irregularity of the pulse, and change in character. These symptoms in most cases ultimately disappear completely. Chronic hydrocephalus, if severe, is usually incurable. Slight degrees of hydrocephalus, on the other hand, usually disappear without leaving any trace of its previous existence. Paralyses do not, as a rule, persist unless they are due to cerebral hemorrhage or involvement of the ganglion-cells of the anterior horn. Deafness and blindness are usually permanent. Psychic disturbances, such as irritability, sudden unprovoked attacks of anger, puerility, weakness of memory, and lack of concentration, are rarely permanent, although they may persist for a considerable period. In the chapter on Treatment we shall discuss, at somewhat greater length, what effect serotherapy has had upon the frequency of the occurrence of the sequelæ.

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CHAPTER XVI

Treatment

History.—Although the life history of the disease is but little over a century, it has had a rich and varied therapeutic career. Chronologically we may divide the history of the treatment of the disease into seven chief periods:

1. Drug therapy.
2. Repeated hot baths.
3. Repeated lumbar punctures.
4. Permanent drainage.
5. Intraspinal injections of antiseptics.
6. Intraspinal injections of diphtheria antitoxin.
7. Specific serotherapy.

In the early days venesection, which was then the ordinary mode of treatment for many acute diseases, was also employed in this affection. Then came the era of polypharmacy, and almost every drug in the pharmacopœia had its one-time champion. The vagaries this disease exhibits in its onset, severity, course, and duration readily account for the warm advocacy of one drug or another by this or that observer. It is but natural that an uncritical observer, who had previously passed through a severe epidemic, should attribute the mildness of a subsequent one to

the administration of a new drug. But, while a comparatively small number of drugs undoubtedly possess some power in relieving a number of the symptoms, it may be safely stated that not one can lay claim to specific or curative action upon the disease.

Similarly we must deny such action to all modes of treatment in use before specific serum therapy entered the therapeutic field. Large claims have been made for some of these methods and each one had more or less vogue for a short time. A larger and more varied experience showed that the high claims were unfounded, and they were soon discarded. Thus it was with the injection of lysol and other antiseptics, and thus with diphtheria antitoxin. Lumbar puncture and hot baths have retained their places in the therapeutic armamentarium, but merely as palliative, not curative measures. Surgical procedures undertaken for the purpose of relieving high intracranial pressure or securing permanent drainage have thus far accomplished little.

Almost hopelessly the medical world passed through the two greatest epidemics in the history of the disease,—the epidemic in New York in 1904–1905 and the one in Prussia in 1905–1907. Despite the use of the most approved methods of treatment, including repeated lumbar punctures and hot baths,

the rate of mortality was as high as or higher than ever before.

Moreover, theoretically there seemed to be little likelihood that the disease would ever be successfully combated by serotherapy. Bacteriological investigations had shown that the meningococcus, unlike the diphtheria bacillus and some other micro-organisms against which antitoxic sera had been successfully employed, did not produce its pathogenic effects through the agency of a soluble toxin secreted by the living organism. But most of the previous attempts at the production of effective immune sera against other infective organisms possessing only endotoxins (*i.e.*, toxins freed only after the disintegration of the bodies of the organisms) had been unsuccessful. As in these cases our aim is not so much to neutralize toxin as to destroy the infective agent, it was found that by merely introducing these sera into the general circulation sufficiently potent effects could not be produced. Though in vitro they possessed definite bacteriolytic and bacteriotropic properties, they failed to exert such action in the body, on account of our inability to bring about sufficient concentration of the immune serum within the immediate vicinity of the organisms.

Undismayed by these unpromising experimental considerations, Kolle and Wassermann and Jochman

in Germany, and Flexner in this country, undertook, practically simultaneously, a series of researches aimed at the production of a serum capable of developing therapeutic action on the meningococcus. But before proceeding to state the important results obtained by these investigators, the fact must be mentioned that Bonhoff and Lepierre had previously produced sera which seemed to possess some protective powers. They labored under the distinct disadvantage of experimenting with small laboratory animals in whom it could not be positively determined whether death was due to infection or intoxication. Moreover, they were not in possession of a method sufficiently accurate for the determination of the biologic properties of their immune sera. The value of the sera thus not being definitely proved, their work created but little interest.

The previous researches of Jaeger, Kolle and Wassermann had shown that, in rabbits and horses immunized with cultures of the meningococcus, there developed a serum possessing well-marked specific agglutinative properties. Loehlin found that this serum also exerted bacteriotropic action. Kolle and Wassermann, who reported their results in the *Deutsche medizinische Wochenschrift* of April 19, 1906, after injecting horses repeatedly with increasing doses of cultures of the meningococcus and aque-

ous extract of the organism, succeeded in obtaining a serum which exhibited considerable protective powers. By the simultaneous or successive injection of aggressins and meningococci, they produced a fatal infection in guinea-pigs, which did not occur previously with the use of the meningococcus alone. When the immune serum was employed either before or after the injection of the aggressins and meningococci, the animals survived. Moreover, by the use of the complement fixation reaction, they demonstrated the existence of specific amboceptors. Their experimental results led them to advocate the subcutaneous injection of this serum as a therapeutic agent in the human infection.

Jochmann's paper, which was published in the *Deutsche medizinische Wochenschrift* of May 17, 1906, describes a serum which he proved experimentally to possess bactericidal and bacteriotropic properties. With this serum were treated 40 cases of meningococcus meningitis at the Ratibor Hospital. Seventeen cases were treated at first with 20 to 30 cubic centimetres of serum injected subcutaneously on the first day and repeated on the third and fourth days. In eleven cases the injections subsequent to the first were made in the spinal canal. Five of the seventeen cases died, three of the deaths being in children who had previously developed hydrocephalus.

In nine cases, six of which received intraspinal injections, there was a critical fall in temperature immediately following the treatment.

Flexner, whose first publication on the subject appeared in the *Journal of the American Medical Association,* August 25, 1906, began his studies with an investigation of the biologic properties of the meningococcus. He showed that the rapid disintegration so characteristic of this organism was due to the action of an intracellular enzyme, and that, as a result of the destruction of the cell bodies, there was liberated a toxin which was capable of producing inflammatory changes in the animal body. He then succeeded in producing in certain species of lower monkeys, among which was the Macacus rhesus, an acute leptomeningitis, by the direct injection of active cultures of the meningococcus into the subdural space, which presented lesions corresponding to those present in the natural disease in man. When he prepared his antiserum he was enabled to test its value on these infected monkeys.

From the first, Flexner realized that, if this antiserum is to exert any beneficial action upon the disease, it must be present in sufficient concentration in the vicinity of the organisms. That this can not be accomplished by introducing the serum subcutaneously becomes evident when we consider the enor-

mous dilution the serum suffers before it reaches the infected meninges. Moreover, it had previously been shown that immune bodies pass but slowly and imperfectly from the blood into the cerebrospinal fluid.

Though Jochmann first advised the intraspinal mode of injection of the serum, the great credit for the general adoption of this method of treatment clearly belongs to Flexner. He not only insisted upon its importance, but offered definite and convincing reasons for his preferring the intraspinal route for the administration of the serum. The failure in Germany to insist on this point and the consequent use of the serum subcutaneously almost led to the abandonment of the serum treatment, as the hopes aroused by its experimental efficacy were greatly shattered by the unsatisfactory results first obtained in the human disease.

The clinical value of Flexner's serum was soon shown by the results obtained with it in Akron, Castalia, Philadelphia, Baltimore, Belfast, and Edinburgh. In Akron, Ohio, of 9 cases of meningitis not treated with serum, 8, or 89 per cent., died; whereas of 11 cases treated with serum, 8, or 72 per cent., recovered. Eliminating two fulminating cases from the latter series, there were left 9 cases, of which 8, or 89 per cent., recovered,—an exact reversal of the previous results. Similarly favorable results were

observed in Castalia and Cleveland, Ohio, as well as in Philadelphia, Baltimore, Belfast, and Edinburgh; so that Flexner and Jobling, in their paper in the January number of the *Journal of Experimental Medicine,* 1908, were able to report 47 cases of meningococcus meningitis treated with antiserum, of which 34 recovered and 13 died,—*i.e.,* 72.3 per cent. recoveries.

PREPARATION OF THE ANTIMENINGITIS SERUM

There are at present in use a considerable number of sera which differ in the mode of their preparation. The sera of Flexner, Kolle and Wassermann, Dopter and Jochmann have been most frequently employed. In this country that of Flexner is almost exclusively used. There does not appear to exist any material differences in therapeutic potency between the sera above mentioned. Horses are employed in the preparation of all of them. The serum of this animal is less injurious to the human body and is obtainable in sufficient quantities.

Flexner's Serum.—Cultures of a large number of strains of the meningococcus killed by heat at 60° C. or in the living state are injected alternately with the autolysate of the organisms. The injections are made once a week in the subcutaneous tissues. On account of the severe symptoms which occasionally

followed the intravenous injections, this mode of immunization had been discarded by Flexner. The subcutaneous injections are made at several separate places at each operation, so as to extend the area of antibody formation and reduce the intensity of the local reaction. The injection is usually followed by a rise in temperature, and local swelling which disappears in a few days. Killed cultures are used during the first month or two.

Kolle and Wassermann Serum.—This is a mixture of three different sera:

1. Serum derived from a group of animals which are first immunized by subcutaneous and intravenous injections with killed and later with live cultures of a number of strains of the meningococcus.

2. Serum from a group of animals repeatedly inoculated with a highly virulent strain of the organism.

3. Serum from an animal that has been repeatedly inoculated intravenously with soluble substances derived from different strains of killed meningococci.

These sera are mixed and heated for one hour at 55° C. on three separate days. To this is added 0.4 per cent carbolic acid as a preservative.

Jochmann Serum.—The animals are inoculated with killed cultures of different strains of the meningococcus. After several months, live cultures are in-

jected. The injections are at first made in the subcutaneous tissues, later intravenously.

Dopter.—The animals are injected intravenously with increasing doses of living cultures of the meningococcus. Aqueous extracts are not employed.

All the sera, with the exception of that of Ruppel, are polyvalent,—*i.e.*, derived by the use of many strains of the meningococcus. The advisability of this mode of preparation is deduced from the marked variations in virulence and agglutinogenic power exhibited by different strains of the meningococcus. The process of immunization usually requires from five to six months. The maximum potency of the serum is usually not reached before one year. To the German and American sera, carbolic acid is usually added as a preservative. Dopter's serum is submitted to artificial aging, a process which he claims tends to reduce the frequency of serum disease. Kept in the refrigerator, the serum usually retains its potency for a long time.

MANNER OF THERAPEUTIC ACTION

Animal experiments and test-tube reactions have shown that the action of the serum is attributable to the presence of a number of immune substances. The most important of these are:

1. Bacteriolysins or antibacterial substances.
2. Bacteriotropins (opsonins).
3. Anti-endotoxins.

1. *Bacteriolysins.*—The serum possesses both direct and indirect bactericidal action. It directly inhibits the growth of the meningococcus, and aids in its disintegration without the intervention of leucocytes. Flexner has shown that weak dilutions have little or no effect, while strong concentrations are highly bactericidal.

2. *Bacteriotropins.*—The experiments of Jochmann, Flexner, and Kolle and Wassermann have demonstrated that the serum markedly stimulates phagocytosis. Flexner has shown that the ingested meningococci are more readily disintegrated than those which have previously not been subjected to the action of the serum.

3. *Anti-endotoxins.*—The serum possesses in a moderate degree the power of neutralizing the endotoxin of the meningococcus. The autolysate loses some of its pathogenic power when mixed with the antimeningitis serum. Its possession of this property is by most of the investigators attributed to the injection of autolysates or watery extracts of the meningococcus in the course of immunization. Dopter, however, claims to have established experimentally that by his method of immunization, in which only

living meningococci are employed, an equal if not greater quantity of anti-endotoxin is developed.

Opinions are still divided as to whether the chief action of the serum is due to its bactericidal or bacteriotropic powers.

In addition to these substances the serum contains antibodies which bind complement, agglutinins, and precipitins. The therapeutic importance of the former has not been definitely determined. The content of agglutinins is no measure of its therapeutic activity. On the presence of precipitins depends the value of the precipito-reaction of Vincent and Bellot.

STANDARDIZATION OF THE SERUM

The serum can not be standardized by the methods employed with the antitoxic sera. Its anti-endotoxic properties can not be used for titration, as its strength is probably not a correct measure of the more important immune principles present in the serum. Moreover, the meningococcus autolysate does not possess uniform and constant pathogenic action on young guinea-pigs and mice, the laboratory animals which are most susceptible to its action. The serum can not be tested against definite quantities of living cultures, on account of the great fluctuations in their pathogenicity. With the exception of Ruppel, whose claims have thus far not been confirmed, no investiga-

tor has succeeded in maintaining the pathogenic properties of the living cultures at a fixed and sufficiently high level.

The determination of the strength of the serum is therefore limited to test-tube reactions. None of these has thus far proved very satisfactory. The complement binding power of the serum has been used by Kolle and Wassermann. It is doubtful if this is a true measure of its therapeutic activity. Flexner and Jobling standardize the serum by determining its opsonic activity. The greatest dilution of the serum at which it still exercises phagocytic action exceeding the controls is taken as a measure of the value of the serum. A standard serum is one which when diluted five thousand times still shows phagocytic activity above the control. Flexner states that the opsonins or bacteriotropins of the serum are highly durable and persist unchanged when kept in the refrigerator for one year or longer.

BASIC PRINCIPLES OF SEROTHERAPY

The bacteriolytic, bacteriotropic, and detoxicating action of the serum can only be exerted when the immune principles on which these effects are dependent are brought in concentrated form in the vicinity of the meningococcus. For this organism produces its pathogenic effects by direct and local

action on the tissues. It does not while living secrete a soluble toxin.

That accumulation of serum in the cerebrospinal fluid in sufficient concentration can not take place by way of the blood is due to two causes: first, the high dilution it suffers in the blood stream; second, the relatively slight permeability of the meninges toward complex substances present in the circulation. This fact has been repeatedly demonstrated. Behring was unable to find diphtheria antitoxin in the cerebrospinal fluid after its introduction in the subcutaneous tissue. Similarly, Quincke failed to find specific immune principles in the cerebrospinal fluid. Mackenzie and Martin have shown that in meningococcus meningitis the cerebrospinal fluid contains neither complement nor bactericidal amboceptors, even when they are abundantly present in the blood. Agglutinins and opsonins were present only in traces. It can therefore readily be seen that by subcutaneous injections of the serum only minimal quantities of the immune principles will reach the site of the inflammation in the meninges.

But while the passage of the immune bodies from the blood into the cerebrospinal fluid is very slow and imperfect, the absorption of these substances from the cerebrospinal fluid into the blood is extremely rapid. Debré, by employing the very sensitive precipitin re-

action for a foreign serum, has shown the rapidity with which absorption takes place. The reaction appeared in the blood about ten minutes after the intraspinal injection of foreign serum. In meningitis the serum passed into the general circulation even more rapidly, showing that the inflamed meninges offer more favorable conditions for absorption.

The rapid elimination of the antimeningococcus serum from the subarachnoid space has been shown by Hohn and Dochez. By determining the protein contents of the cerebrospinal fluid, Hohn found that the serum is for the most part absorbed within twenty-four hours. Similarly Dochez, by estimating the antiproteolytic ferment in the serum, showed that it tends to disappear from the cerebrospinal fluid within twenty-four hours.

The practical deduction to be drawn from these experimental facts is obvious: if the serum is to exert its maximum effect on the disease, it must be introduced directly into the spinal canal at frequent intervals until such time as all the meningococci are destroyed. The frequent injections are necessary to make good the loss in concentration of the serum sustained by its rapid absorption into the blood. We shall see that these are the principles which guide us in the administration of the serum.

TECHNIC OF SERUM ADMINISTRATION

The proper procedure for performing lumbar puncture has been described in detail in a previous chapter. As soon as the pressure in the subarachnoid space has reached the normal level, the manometer is detached and the cylindrical funnel of the Quincke set attached, the tubing being lowered in the process so as to keep it filled with cerebrospinal fluid (Fig. 29). The funnel is then filled with the desired quantity of antimeningitis serum, which had previously been warmed up to the body temperature by placing the vial containing the serum in hot water. The funnel is held at such a level as to permit the slow passage by gravity of the serum into the subarachnoid cavity. The time consumed in the process naturally varies with the amount of serum introduced, but should rarely be less than ten minutes. It is extremely important to keep the needle in the same position throughout the whole procedure, and thus prevent displacement of the point of the needle from the spinal canal. The injection would then no longer be a subarachnoid, but rather an epidural or subcutaneous one, which, as we have seen, is practically valueless.

The serum furnished by some American manufacturers is put up in syringes, which are attachable

FIG. 29.—Apparatus for administration of antimeningitis serum.

to the puncture needle by a short piece of rather too wide tubing. Personally we do not recommend the use of a syringe for the introduction of the serum into the spinal canal. The injection is usually too rapid and irregular, and undue force may be exerted, causing severe compression symptoms. By the use of gravity, this can generally be avoided, as the fluid runs in more uniformly and slowly. Moreover, the rhythmic changes in the pressure in the subarachnoid space due to circulatory and respiratory movements are not forcibly overcome, as is the case when the serum is injected by syringe.

The condition of the patient must be very closely watched by a competent assistant and the operator immediately informed of any change in the character of the respiration and pulse, or of the appearance of cyanosis, dilatation of the pupils, or stupor.

After the needle is withdrawn, the side of the puncture is covered with a sterile piece of gauze and adhesive plaster, the patient's head kept low and buttocks raised for ten minutes. The patient is then placed in bed, the foot of which is kept raised (8 to 12 inches) for several hours. This procedure, first advised by Jochmann and Schoene, and regularly employed by Levy, seems to aid the passage of the serum into the cranial cavity and its diffusion through the whole subarachnoid space and ventricles. The patient

must be carefully watched for at least fifteen minutes by a physician for the appearance of apnœa or other symptoms of collapse. We have recently adopted the practice of performing artificial respiration for a short time on all cases subsequent to the injection of serum. In this manner we have apparently succeeded in preventing the occurrence of dangerous apnœa.

Some authors advise the preliminary injection of morphine in order to avoid the great restlessness often exhibited by patients during this treatment. In children at least, we have not found occasion to employ this drug. General anæsthesia is contraindicated, as it is a procedure attached with considerable danger. It should be employed only when the unusual violence of the patient would otherwise prevent the performance of the puncture.

In this connection we must speak of the mode of controlling the injection of the serum advised by Sophian. He found a drop in blood-pressure as soon as the injection of serum in the subarachnoid space is begun. This continues steadily as more and more serum is introduced. After the mercury has dropped 20 to 30 millimetres, the continuance of the injection leads to rapid and sudden further lowering of the blood-pressure. He cites the case of a robust adult in whom there occurred a drop of 30 milli-

metres of mercury after the injection of only 12 cubic centimetres of serum. On injecting 3 cubic centimetres more of serum, his blood-pressure dropped 30 millimetres more at one bound, making a total drop of 60 millimetres of mercury. The clinical signs at the time did not indicate shock, the pulse continued to be fair but rapid, the color good, but the breathing was shallow and somewhat irregular. A few minutes later the patient suddenly stopped breathing, which was soon followed by cessation of heart action. Death was apparently prevented only by the adoption of active measures.

Sophian's usual technic is to have an assistant take blood-pressure readings throughout the whole operation. The withdrawal of cerebrospinal fluid is stopped when the arbitrary drop of 10 millimetres of mercury has taken place. The serum is then allowed to run in slowly by gravity, the funnel being raised or lowered to regulate the rate of flow. The injection is discontinued when in an adult, whose average blood-pressure is 110 to 130 millimetres, a total drop of 20 millimetres of mercury has taken place. By using this method of controlling the amount of serum injected, he has found that the average dose of serum is considerably smaller than that usually advised, being only about 20 to 25 cubic centimetres in adults. Despite these small doses, his

results have been very good. His observations being based on about 200 cases, the method would seem to deserve further trial. We have had no personal experience with this mode of controlling the administration of the serum. It would seem to us that in infants and young children, the marked restlessness so often present during the operation would seriously interfere with the accuracy of the blood-pressure readings.

ROUTINE METHOD OF TREATMENT WITH SERUM

We should always have a supply of serum ready to inject when performing a lumbar puncture on an acute case. The serum should be injected at once, if the fluid withdrawn is purulent or turbid, without waiting even for a microscopic examination. If the fluid is clear, a smear preparation should be made and stained by the Gram stain. If meningococci are not demonstrable, we must be guided by the clinical symptoms, bearing in mind that clear and sterile fluid is not infrequently present in the first twenty-four hours of the disease. While the injection of serum in a non-meningococcus meningitis will do no good whatsoever, it at least will do no harm. On the other hand, should the case subsequently prove to be one of meningococcus meningitis, the injection of serum at the first puncture might be of incalculable

value to the patient. Our duty to inject serum is clear, if there is the least doubt lurking in our mind as to the nature of the case. Should the bacteriological examination of the fluid show the presence of organisms other than the meningococcus, no further injections of serum are given. In mixed meningococcus infections the procedure is the same as in pure infections.

All observers whose opinions are based upon large experience with the serum treatment are now in practical accord as to the method which yields the best results. In malignant cases the injection should be repeated within twelve hours. There is a theoretical objection to the use of the serum in these cases in the possible liberation of a large amount of endotoxin, as a result of the rapid disintegration of the meningococci brought about by the bacteriolytic action of the serum. But such consideration should not lead us to withhold the possible benefits of serotherapy from any patient, no matter how desperate the condition is. By employing it in apparently hopeless patients, the case for the serum is not placed in as favorable a light as it would be if these were excluded. The serum, however, is no longer on trial, and the literature shows that occasionally recovery has taken place even in desperate cases.

In cases of ordinary severity, we should inject

three or four full doses at twenty-four-hour intervals. Even should marked amelioration of the clinical symptoms appear, it is not advisable to discontinue the injections before the three consecutive daily treatments have been given. By the adoption of this systematic mode of treatment, we can best guard against the occurrence of a relapse.

There is experimental justification for the repetition of the injections at comparatively short intervals in the rapidity with which the cerebrospinal fluid rids itself of the foreign serum. Unless, therefore, the supply of fresh serum is kept up by repeated injections, its concentration becomes so rapidly reduced that it soon fails to exert in full its beneficial effects. In very mild cases one dose may be sufficient to destroy all the meningococci. In most cases, however, a single injection is inadequate to accomplish this result. Moreover, it is of the utmost importance to achieve this result in one continuous course of treatment, otherwise a relapse may occur after a long interval, and we may be compelled to administer the serum in the anaphylactic state and run the risk of the appearance of dangerous symptoms.

The first systematic series of three or preferably four consecutive daily injections having been given, the subsequent course of treatment to be pursued will

depend upon the clinical symptoms present and the character of the cerebrospinal fluid. Ordinarily at this time the temperature will be normal, the mental condition greatly improved, and the hyperæsthesia and rigidity considerably less marked. The most trustworthy indication, however, that the infection has been overcome is given by the cerebrospinal fluid. Usually at this stage it is clear, the adventitial cells have disappeared, and the polynuclears are largely replaced by lymphocytes. When the cerebrospinal fluid has assumed this character and the meningococci are no longer demonstrable, we may conclude that the infection is definitely terminated and that no further serum treatment is required.

The persistence of meningococci in the fluid demands the continuance of daily serum injections until such time as they shall have disappeared. It may require a dozen or more injections to bring this about, but, unless this result is achieved, there is no certainty that the patient has escaped the danger of a possibly fatal relapse. Such an eventuality can not fairly be charged to the inefficacy of the serum when it is clearly due to insufficient treatment. The fear of employing too large a (total) quantity of serum must not deter us from persisting with the treatment until a definite cure is achieved.

Should, at any period of the disease, symptoms

indicative of a recrudescence appear, such as fever, headache, hyperæsthesia, or accentuation of the rigidity, a lumbar puncture must at once be performed. If the meningococcus is found to have reappeared, the systematic course of treatment identical with that employed during the primary attack must be instituted.

Even in the absence of symptoms presaging a relapse, it is advisable to repeat the punctures at intervals of about five days up to the time when the cerebrospinal fluid has assumed its normal character (including normal pressure). By so doing, we may occasionally detect the earliest beginning of a relapse at a time when it is still clinically latent, and thus cut short its course by judicious treatment.

Case.—H. K., age 11 months, admitted January 1, 1913.

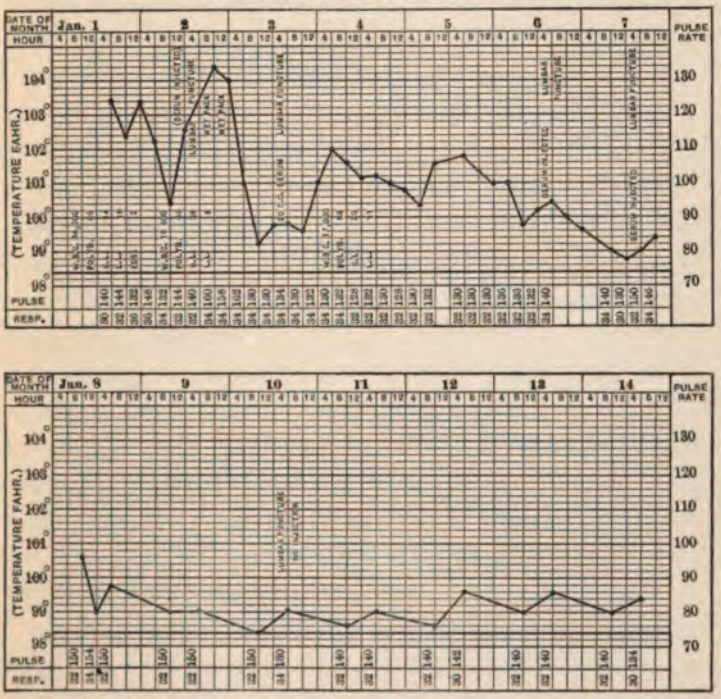
Family History.—Negative.

Past History.—Scalp wound five months ago which quickly healed. Full-term child; breast fed.

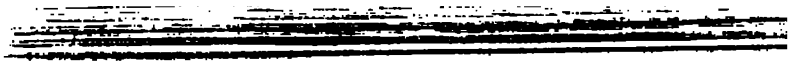
Present History.—Onset four days ago with convulsions; apathy then persisted for three days, except for slight periods of consciousness, during which child was highly irritable. Projectile vomiting during first three days, at times very frequent. No constipation.

Examination.—Marked Macewen, marked cervical rigidity. Internal strabismus, bilateral Babinski, Oppenheim; no Kernig. Slight tenderness along spine.

CHART III



Repetition of Lumbar Puncture after an Interval of Five Days to ward off a Possible Relapse.



Leucocytes 34,000; polynuclears 68 per cent.; small lymphocytes 14 per cent.; large lymphocytes 16 per cent.; eosinophiles 2 per cent.

January 2: Lumbar puncture: 25 cubic centimetres subarachnoid fluid removed, and 20 cubic centimetres of Flexner's serum injected. Examination of fluid: albumin 4 mm.; reduction 0; cytology, polynuclears 96 per cent., mononuclears 4 per cent.; bacteriology, contaminated. Temperature 104.4° F.; pulse 158; respiration 34.

January 3: Lumbar puncture: 20 cubic centimetres of subarachnoid fluid removed, and 20 cubic centimetres of Flexner's serum injected. Examination of fluid: albumin 8 mm.; reduction 0; cytology, polynuclears 100 per cent.; bacteriology, few Gram-negative extracellular bacilli; cultures negative. Temperature 101° F.; pulse 130; respiration 34.

January 7: Lumbar puncture: 20 cubic centimetres of subarachnoid fluid removed; 20 cubic centimetres of Flexner's serum injected. Examination of fluid; cytology, no cells in sediment; albumin 6 mm.; reduction 0 (Fehling's); bacteriology, spreads negative, no growth in media. Temperature 99° F.; pulse 130; respiration 30. Marked changed for the better in child's general condition.

January 10: Lumbar puncture: about 70 cubic centimetres of cerebrospinal fluid withdrawn; first specimen blood tinged; second clear. Examination of fluid: albumin 2 mm.; reduction present; cytology, bloody sediment; bacteriology, spreads and cultures negative. Temperature 99° F.; pulse 130; respiration 34. General condition good; no hydrocephalus; no rigidity to any extent; distinct strabismus; no Kernig; slight urticaria, probably due to serum.

INTRAVENTRICULAR INJECTION OF SERUM

Though in the large majority of the cases the serum reaches in sufficiently concentrated form every part of the nervous system that is bathed by cerebrospinal fluid, there are cases, especially in infants, where the lack of any favorable influence on the course of the disease gives us reason to believe that some important focus of infection has not been reached by the serum.

In most of these cases the communication between the ventricles and the spinal subarachnoid space is shut off by functional or organic obliteration of the outlets of the fourth ventricle, so that the serum injected in the lumbar cul-de-sac is prevented from reaching the infected ventricles. Aside from the evident inefficacy of the serum, we may suspect the existence of this condition if, despite demonstrable signs of hydrocephalus, very little fluid is obtainable by lumbar puncture. Moreover, contrary to what is the case when the communication between the cranial and spinal cavities is free, there is no increase in the pressure of the fluid when the patient is changed from the recumbent to the upright position.

In these cases the intraspinal injection of serum, at least as far as the infection of the ventricles is concerned, is quite as devoid of value as is its sub-

cutaneous administration. We can only reach the focus of infection by direct intraventricular injection of the serum. In these cases it is desirable to tap each lateral ventricle on alternate days, as occasionally the communication between them is obliterated.

Technic (Figs. 30 and 31).—This is not attended with unusual difficulty when the fontanelle is still open. The scalp over the anterior fontanelle is shaved and rendered surgically aseptic in the usual manner or by the use of tincture of iodine. The needle, which is about 8 centimetres long, is inserted near the lateral angle of the fontanelle, about 2.5 centimetres from the median line, and is gently pushed downward and slightly inward toward the median line to a depth of about 3 centimetres, when the cerebrospinal fluid will usually begin to flow. When this has ceased, a quantity of serum usually considerably less than the amount of fluid withdrawn is then allowed to flow in by gravity. In older children and adults a trephine hole is made at a point 3 centimetres above and behind the external auditory meatus (Keene's point) before tapping the ventricles.

In the Children's Service of Dr. Koplik, intraventricular injection of serum was performed upon eight cases. In some the lateral ventricles were irrigated with a weak Gram solution previous to the administration of the serum. All the cases ended

fatally. Intraventricular administration of serum was also unsuccessful in the hands of Cushing and Netter. Up to the present time only three successful cases are reported in the literature; one by Fischer, another by Triboulet, and a third by Levy.

Posterior Basic Type.—L. N., age 5½ months; admitted June 25, 1910; died August 1, 1910.

***Family History.*—Negative.**

***Past History.*—Diarrhœa for last two weeks.**

***Present History.*—Sudden onset four days ago with high fever. Child very irritable. Next day child vomited after each feeding (not stated whether projectile or not), and same evening had a convulsion. Since then fever has persisted. Respirations rapid. Child apathetic unless disturbed.**

***Examination.*—Child sleeps most of the time; irritable** when disturbed.

Face: Shows weakness of left side. Left orbital aperture larger than right and eye does not close completely.

Head: Shows marked Macewen. Fontanelle bulging and tense. Neck shows slight rigidity.

Pupils equal and regular. No ocular palsies.

Skin shows no tache.

Extremities: Right leg moved less than left. Slight rigidity of right leg. Slight bilateral Kernig.

Clinical Notes.—June 30: Flatness of right side of face.

July 2: Lumbar puncture: 20 cubic centimetres withdrawn under slight pressure. Fluid cloudy; found to contain meningococci; 15 cubic centimetres of Flexner's serum in-

jected at once. Child comatose during procedure. Artificial respiration necessary.

July 3: Temperature up to 104° F. Child very irritable. Head retracted, but no rigidity of neck. Marked tache.

July 4: Lumbar puncture: 15 cubic centimetres of cloudy fluid withdrawn; 15 cubic centimetres of Flexner's serum introduced.

July 5: Anterior fontanelle tense. Weakness of right face the same. Circumference of head 44 centimetres. Lumbar puncture: Introduction of 30 cubic centimetres of Flexner's serum. General condition good. Leucocytes 22,600; polymorphonuclears 77 per cent.

July 9: General condition worse. Anterior fontanelle tense and pulsating. Head circumference 43½ centimetres. Very irritable, marked tache and Kernig. Temperature ranged from 104° F. to normal.

July 11: Brain puncture (lateral ventricles) and lumbar puncture by Dr. Elsberg. Cloudy fluid from both. No organisms found. Serum injected into spinal canal and ventricles.

July 12: Temperature stayed down to-day. General condition somewhat better.

July 13: Head same size, 43½ centimetres.

July 15: For past three days temperature has gone up to 103–104° F. in evening. General condition worse. Kernig and opisthotonus marked.

July 16: Brain puncture (Dr. Elsberg) and lumbar puncture (Dr. Heiman). 75 cubic centimetres of turbid fluid removed, and canal irrigated via ventricles with saline

solution colored with methylene blue; 30 cubic centimetres of Flexner's serum injected into canal. Child went into mild state of collapse, but recovered after a few hours.

July 17: Signs of posterior basic pressure less marked. Still considerable neck rigidity and Macewen. Depression of right angle of mouth. Slight tache and Kernig. Knee-jerks have reappeared. Child less irritable; takes feedings well.

July 18: Leucocytes 13,200; polynuclears 64 per cent.

July 19: Circumference of head 43 centimetres.

July 25: General condition slightly better. Head increasing in size. Circumference 44 centimetres.

July 28: Brain puncture by Dr. Elsberg: Impossible to get fluid from lateral ventricles after repeated punctures. Finally needle inserted into third ventricle, and orange-colored turbid fluid withdrawn under high pressure. Lumbar puncture by Dr. Heiman: Few drops slightly turbid fluid obtained. Irrigation from above with saline methylene-blue solution. After fifteen minutes the lumbar fluid began to flow faster, but it was not colored blue.

July 30: Lumbar puncture: 70 cubic centimetres of clear fluid withdrawn under considerable pressure; 30 cubic centimetres of serum injected. Child reacting well.

August 1: General condition worse. Pulse weak and rapid. Twitching of extremities. Ceased to breathe.

USE OF SERUM IN COMPLICATIONS

Recently the serum has also been employed in a number of complications of the disease. Ladd after

FIG. 30.—Intraventricular puncture and injection of serum in an infant. Position of needle. (Netter and Debré.)

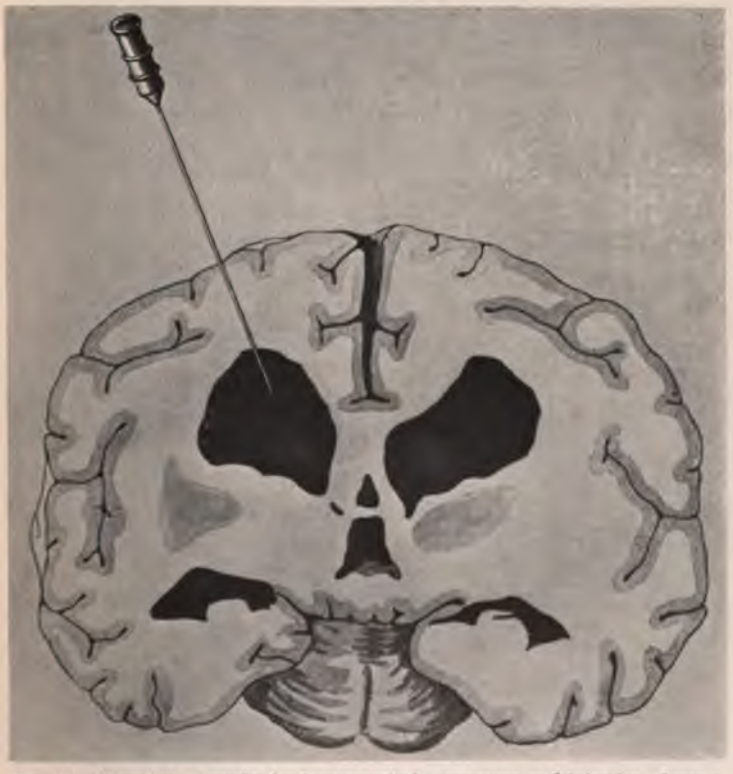


FIG. 31.—Direction of needle for intraventricular puncture and injection of serum. (Netter and Debré.)

aspirating the inflammatory exudate directly injected the serum into the affected joint. This was followed by rapid improvement in the condition. In two cases of meningococcæmia, one by Bovaird and the other by Netter, intravenous injection of the serum resulted in recovery. The serum has also been successfully employed in conjunctivitis due to the meningococcus.

DOSAGE

The dose of serum is measured by volume. We have no definite measure of the efficiency of the serum, as is the case with diphtheria and tetanus antitoxins. It is rarely advisable to introduce a larger volume of serum than cerebrospinal fluid withdrawn. In cases where only a few drops of thick pus are obtainable, it is our custom to inject five or ten cubic centimetres of serum. At the next puncture we have frequently found that considerable liquefaction of the purulent exudate has taken place in the interval. In infancy we usually inject ten to fifteen cubic centimetres. In adults thirty to forty cubic centimetres are usually well borne. As no force is employed in introducing the serum by the gravity method, symptoms of compression are rarely exhibited.

The total quantity of serum used varies greatly.

In protracted cases as much as 800 cubic centimetres have been injected. Netter and Debré have shown that the total quantity of serum injected does not play an important rôle in the frequency or severity of the serum disease.

RESULTS OF SERUM TREATMENT

When the nature of the disease is borne in mind, it need not greatly surprise us that the early clinical reports on the action of the serum were regarded with considerable scepticism. Even Flexner, who had proved its efficacy in experimental meningitis, expressed himself with great reserve. A disease showing a mortality which may vary from 30 to 80 per cent. evidently does not present very favorable conditions for the exact valuation within a short time of any therapeutic agent.

Moreover, when the serum was first employed, the epidemic outbreaks both in America and Germany had largely subsided. But, as has been repeatedly stated, at such a period the disease spontaneously assumes a greatly attenuated character. So it was but natural that the lower death-rate seen in the earlier cases treated with serum should have been largely attributed to the decline of the epidemic.

With wider and more varied experience, how-

ever, it soon became evident that at last we were in possession of a potent specific agent for combating this dread disease. The first convincing proof of the efficacy of the serum came when it was for the first time employed at the height of a very severe and extensive epidemic, as was the case at Belfast and Edinburgh. When it was employed somewhat later in Paris, its efficacy at the beginning of an epidemic — *i.e.,* at a period when the disease usually exhibits its maximum intensity—was also shown. Its potency was again in evidence in the recent epidemics in the Southern States. At the present time the curative value of the serum has become so firmly established that we need hold no brief for its use in meningococcus infections.

The large body of observations now extant in the literature shows that the serum is efficacious in reducing the mortality, lessening the severity, shortening the duration, and reducing the frequency of the complications and severity of the disease.

Effect on Mortality.—Practically all observers who have employed the serum intradurally in sufficient dosage attest to the fact that a notable reduction in the mortality has been the result. The following table, which is based upon a number of sources, shows this convincingly.

ENINGOCOCCUS MENINGITIS

Reported by—	Serum used.	Cases treated with serum.		Percentage mortality of cases treated without serum.
		Number.	Percentage mortality.	
Flexner (collective)	Flexner serum	1294	30.9	70–80
Netter		100	28	49
Rob		90	30	72.3
Ker		30	43	80.5
Koplik		15	13.3	60
Dunn		40	22.5	70
Chase and Hunt.		12	25	90
Sladen		23	13	64
Fulton		22	31	78.4
Ladd		31	35.5	?
Levy	Kolle and Wasserman serum	165	18.18	52.14
Leick		34	32.4	66
Neglein		30	26.6	50
Kleinschmidt		21	19	62.47
Quenstedt		18	22.2	56.2
Dopter (collective).	Dopter serum	402	16.44	65
Schoene	Jochmann serum	30	25	53
Jehle	Paltant serum	41	45	70
Weiss-Eder		23	39	85

This table gives the gross mortality and includes among the serum-treated cases a number of deaths in patients moribund when the treatment was instituted. Moreover, in a considerable number the treatment was not sufficiently vigorous or persistent. Included also are deaths from complications which had nothing to do with the disease.

Despite this, a comparison with the cases in the same vicinity not treated with serum shows that the mortality was generally reduced to one-half, and not uncommonly to one-third or one-fourth.

In this connection it is interesting to study the distribution of the fatalities at various age periods. There are available for this purpose the tables of Flexner, Netter, Dopter, and Levy, which are given below.

	Flexner.			Netter.			Dopter.
	No. of cases.	Deaths.	Percentage of mortality.	No. of cases.	Deaths.	Percentage of mortality.	Percentage of mortality.
Less than 1 year.....	129	64	49.6	18	15	61	48.6
1–2 years.....	87	27	31	15	4	26.6	20.1
2–5 years.....	194	55	28.4	22	6	27.2	9.3
5–10 years.....	218	33	15.1	21	2	9.5	8.5
10–20 years.....	360	106	29.4	11	2	18.1	10.2
Above 20 years.....	288	108	37.50	13	3	23	14.1

The highest mortality was seen in the first two years of life. This is partly attributable, according to Netter and Debré, to the difficulties encountered in establishing the diagnosis at an early date. Moreover, at this age there is a tendency to the rapid development of a hydrocephalic condition. Yet even

at this age a considerable reduction in mortality has been effected. The rather high mortality in adults seen in Flexner's collective results is not so noticeable in those of Netter and Dopter.

Our own results cover 49 cases treated with Flexner's serum at the Mount Sinai Hospital, 42 of which were admitted to the Children's Service of Dr. Koplik.

The mortality at the various age periods was as follows:

	Cases treated with serum.			Cases not treated with serum.		
	No. of cases.	Deaths.	Percentage of mortality.	No. of cases.	Deaths.	Percentage of mortality.
Up to 1 year	14	9	64.29	10	7	70
1–2 years	14	8	57.14	7	5	71.43
2–5 years	8	0	0	10	4	40
5–10 years	6	0	0	23	11	47.82
Above 13 years	7	1	14.28			

We thus see that, while up to two years of age the reduction in mortality was but slight, it was strikingly evident in the ages between two and thirteen years. There was not a single fatality in the fourteen cases of this period, whereas the mortality at this age period varied between 40 and 47.82 in the 33 cases

treated between 1905 and 1908. It must be added that the diagnosis was established by the demonstration of the organism in the cerebrospinal fluid.

The importance of beginning the treatment as early as possible in the course of the disease is strikingly shown by the figures of Flexner, Netter, Dopter, and Levy.

	Levy.			Netter.			Flexner.	Dopter.
	No. of cases.	Deaths.	Percentage of mortality.	No. of cases.	Deaths.	Percentage of mortality.	Percentage of mortality.	Percentage of mortality.
1st day	6							
2d day	33	3	9.09	44	9	20.9	18.1	8.20
3d day	37	7	18.91					
4th day	24	4	16.66					
5th day	14	3	21.43	32	11	33.3	27.2	14.40
6th day	11	3	27.27					
7th day	9	3	33.33					
After 1st week	26	7	26.92	23	6	26	36.5	24.1

The figures of Levy exhibit the remarkable influence the date of the first injection has on the prognosis of the disease. Of 39 cases treated in the first two days only 3 died, and these within thirty-two hours. On the third day the mortality was double that of the second. From the fourth to the seventh day, it increased about 6 per cent. each day.

The analysis of the 712 cases at the various age periods, according to the day of first injection, is given in a very instructive table by Flexner.

Day of injection.	Percentage mortality.					
	1–2 years.	2–5 years.	5–10 years.	10–15 years.	10–20 years.	Over 20.
1st to 3d day	7.7	20.0	10.9	13.4	13.4	41.2
4th to 7th day	24.3	25.8	11.6	31.1	31.1	40.0
Later than 7th day	49.1	37.3	20.8	32.7	32.7	38.4

It appears that the effect of the time of the first injection is of most importance in the first two years of life. Injected on the first to the third day, the remarkably low percentage mortality of 5.6 was obtained. The mortality rose to 31.2 per cent. in the cases injected from the fourth to the seventh day. At a period later than this 60 per cent. of the cases died,—*i.e.*, a death-rate approaching that seen in the ante-serum days.

The supreme importance of early diagnosis and treatment in this group of cases, which usually forms the largest contingent of an epidemic, can not well be better shown. When we consider that at this tender age the delicate structures of the brain offer little resistance to the inflammatory process, and that hydrocephalus readily develops as a result of the rapid formation of adhesions at the base and the

yielding character of the cranial coverings, it need not surprise us that the slightest delay in the adoption of specific treatment should seriously compromise the chances of recovery.

Effect on the Symptoms.—The serum may influence all or only a part of the symptoms, according as the one or the other effect takes place. Levy, whose experience with serotherapy has thus far been the most extensive of any single observer, divides the cases into three types.

In the first type, which forms the largest contingent of the cases, the introduction of the serum is soon followed by a drop in temperature to the normal either by lysis or crisis, improvement in the general condition, diminution of the hyperæsthesia, heachache, and restlessness, disappearance of delirium and insomnia, and return of appetite for solid food. The characteristic rigidity of the neck and Kernig sign may, however, persist for several days or a week after all the other symptoms have completely disappeared.

In the second type a favorable effect is shown on all the symptoms except the fever, which remains at the same level or even shows a tendency to rise after each injection. After a few days the temperature also comes down to normal, and recovery is complete.

In the third type the injections are not followed

immediately by any clinical evidence of improvement. After a few days the patient begins to show signs of improvement, which is very gradual.

According to Flexner, there is a critical cessation of symptoms in about 30 per cent. of the patients that recover. With the amelioration in the symptoms, there is usually associated a diminution in the degree of polynuclear leucocytosis of the blood.

Effect on the Cerebrospinal Fluid.—The best index of the effect of the serum on the disease is to be found in the cerebrospinal fluid. The reason for this is happily expressed by Levy thus: "In no disease are we presented with such favorable conditions for the study of the action of a therapeutic agent on the causative organism and the local inflammatory changes produced by it, as in meningococcus meningitis. The treatment takes place under ideal experimental conditions. It may truly be said that the cerebrospinal canal is a sealed test-tube, for the experiments of Quincke and v. Behring show that not only do not foreign substances pass into the cerebrospinal fluid, but also such complex substances as the immune bodies which are formed in the body itself. The canal, therefore, is influenced neither from within nor from without. In this space, filled with fluid containing meningococci, we introduce the serum and

allow it to act at body temperature on the organisms with which it comes in direct contact. At the next puncture we have the opportunity of studying under ideal conditions the changes that have taken place in the interval. No test-tube or animal experiment affords better opportunity for arrival at a definite conclusion.

Macroscopic.—The consistency and cloudiness of the fluid usually diminish with each successive injection. And it is not at all uncommon for the fluid to assume its normal appearance after the first series of consecutive injections.

Protein Contents.—Despite the fact that the fluid is temporarily enriched by the introduction of the serum, the protein percentage diminishes from day to day in favorable cases. The quantitative estimation of the proteins during the course of the treatment is, therefore, a delicate index of the regression of the inflammatory process.

Cytologic Changes.—The effect of the serum is first shown in the disappearance of the large adventitial cells. The next change occurs in the polymorphonuclears, which greatly diminish in number and become less degenerated. With the diminution in the polymorphonuclears there occurs simultaneously a relative increase in the lymphocytes. At a later

stage these cells also diminish and the fluid assumes its normal character. The replacement of the polymorphonuclears by the lymphocytes occurs also in non-serum cases when they show a tendency to verge toward chronicity. In the serum cases, however, these changes occur in a short time, and indicate the subsidence of the inflammatory process.

Effect on the Meningococci.—The changes in the meningococci demonstrable after the injection of the serum supply the last link in the chain of proof demanded by those who remain unconvinced of its efficacy by the abundant statistical data. In most of the cases their number is greatly diminished and the viability on artificial culture-media lost after the first injection. They become swollen or fragmented and show great variability in staining. As a rule, the number of extracellular organisms diminishes first. The phagocytic leucocytes do not show the evidences of degeneration which are usually seen when serum has not been employed. This is another indication that the ingested meningococci have partly lost their vitality. The meningococci usually lose entirely the ability to take the stain after the third injection, so that they are no longer demonstrable in smear preparations. Levy gives the following figures as to the time of their disappearance:

In 18 cases after the first injection,
In 33 cases after the second injection,
In 35 cases after the third injection,
In 14 cases after the fourth injection,
In 9 cases after the fifth injection,
In 4 cases after the sixth injection,
In 1 case after the eleventh injection.

Relapses.—All observers who have treated the disease in the systematic manner described above have noted the paucity of relapses. Indeed Levy has seen so few relapses that, when an apparent relapse occurs after ten days of complete absence of symptoms, he looks very carefully for evidence of serum disease. It is a serious therapeutic error to inject serum in such a case without a very thorough microscopic examination of the cerebrospinal fluid. In one of his cases fatal anaphylactic shock resulted.

Effect on the Duration of the Disease.—We have seen that the duration of the disease, both in the fatal and recovered cases, is very variable. In 123 fatal cases, Netter found that the disease persisted for more than one month in 77 and for more than two months in 31. In 83 recovered cases it lasted more than one month in 37 and more than two months in 20. The average duration was 30 days. In 350 cases of the recent epidemic in New York (before the introduction of the serum), Holt found that the

disease lasted one week or less in only 3 per cent., and five weeks or longer in 50 per cent.

An analysis of 228 serum-treated cases by Flexner showed that the duration of active symptoms, but not including the time required for the disappearance of the rigidity of the neck and the Kernig sign, after the first injection was approximately eleven days.

Levy found that the average duration in 127 of his recovered cases was 12.5 days. The average duration after the first injection was only 6.86 days. He considers the disease terminated when the fever and symptoms have disappeared, and the cerebrospinal fluid shows no marked changes from the normal character and no longer contains meningococci.

Effect on the Complications and Sequelæ.—While these have varied greatly in different epidemics, it is usually estimated that they occur approximately in 20 to 25 per cent. of the cases. Netter, before the use of the serum, found permanent after-effects of the disease in 23.5 per cent. In the Silesian epidemic they occurred in 25 per cent.

Since the adoption of serum treatment, Netter has observed such sequelæ in only 6.3 per cent., Dopter in 6.2 per cent. In 295 recovered cases Flexner reports only 3.4 per cent. This observer, in his most recent publication, gives a table on the occur-

rence of impaired hearing and vision and arthritis in serum-treated cases, which we here reproduce.

	Day of disease of first serum injection.									
	1st day.	2d day.	3d day.	4th day.	5th day.	6th day.	7th day.	2d week.	3d to 8th week.	Totals.
Number of cases in which deafness occurred.....	1	15	6	5	3	3	1	7	4	45
Number of cases in which impaired vision occurred..	1	..	..	2	2	..	..	3	4	12
Number of cases in which arthritis occurred.....	..	5	3	1	..	..	..	2	..	11

Deafness was complete in 39, and partial in 6.

Blindness occurred 3 times.

Impaired mentality was seen 3 times.

Paralysis occurred in 11 cases as follows: Strabismus in 5; lower extremity 3; of the face in 2; and of the shoulder in 1. It can be seen that of all the severe sequelæ, hearing remains the least influenced (3.5 per cent.).

Levy, who observed after-effects in 15.5 per cent., attributes his higher figures to the fact that many of the complications were already developed at the time the patients were admitted to the hospital. The most common after-effects were deafness and blindness. All forms of paralysis present in the height of the disease resulted in complete functional restoration.

Levy did not observe any cases in which idiocy, imbecility, or even milder psychical changes appeared after the patients left the hospital.

Serum Disease.—This condition, which was first described under this name by v. Pirquet and Schick, is one commonly seen after the subcutaneous injection of diphtheria antitoxin. It is due to the introduction of foreign serum in the circulation. It seems that, when foreign serum is injected by the intradural route, serum disease occurs even more frequently than when introduced subcutaneously. In serum-treated cases this condition develops in about one-third or one-half of the cases, whereas in diphtheria it occurs in only about 15 per cent. of the cases. The symptoms usually appear from eight to ten days after the first injection in the form of fever, urticarial or erythematous eruption, arthralgia, regional enlargement of the lymph-nodes, digestive disturbances, and albuminuria. These symptoms occur somewhat less frequently in the infant than in the older child or adult. Netter and Debré have shown that the total amount of serum injected does not greatly influence the frequency, time of appearance, or severity of the serum disease.

When, however, the injection is given in the anaphylactic state (*i.e.*, a week or more after a previous subcutaneous or intradural injection of a foreign

serum), much more severe symptoms may appear within a few hours. The eruption, which is more marked, may be accompanied by high fever, chill, prostration, and intense dyspnœa due to œdema of the glottis and trachea or pulmonary œdema. Usually they subside in a short time and do not lead to serious results.

In a small number of cases, which have been well described by Netter and Debré, the serum disease may manifest itself in the form of meningeal œdema, analogous to the laryngeal œdema occasionally seen in the convalescence from laryngeal diphtheria. The selective localization in these cases is probably due to lack of resistance on the part of the previously inflamed tissues.

There is a sudden rise of temperature, general malaise, restlessness, and insomnia. The rigidity of the neck and Kernig sign, which may have disappeared or become attenuated, appear once more or become greatly accentuated. Relapse is suspected, especially as an urticarial eruption is frequently absent. Recognition of the true nature of the condition is extremely important, as failure to do so may lead to the adoption of a mode of treatment which seriously jeopardizes the patient's life. A correct diagnosis is made by lumbar puncture, which shows

clear fluid containing few cells and no meningococci. The condition clears up within a short time.

Should, however, serum be injected under the mistaken idea that a relapse is threatened, the symptoms will become greatly aggravated within a few hours, as we would then be treating serum disease with serum. In one such case Levy saw a fatal result occur.

Untoward Results from Serum Administration.—Restlessness, vertigo, vomiting, painful sensations in the lumbar region and lower extremities, vesical and rectal tenesmus are occasionally seen during or immediately after the administration of the serum. The local symptoms are probably due to stretching of the lower nerve-roots by the injected serum. In a certain number of cases there appears, during the operation or immediately after, a train of symptoms indicating shock. Several factors may be concerned in its causation,—too great or too sudden change in cerebrospinal pressure, rapid liberation of endotoxins, or hypersensibility to the foreign serum. The earliest and most important symptom indicating the approach of shock is a change in the character of the respiration. The breathing becomes slow, shallow, and irregular. Occasionally it is deep and stertorous. With this there are often associated pallor or cyanosis, dilation of the pupils, general relaxation, convulsive

movements of the face and limbs, and stupor. The pulse, while usually feeble and irregular, is occasionally very deceptive, as it will continue to be fair when the respirations have become markedly altered in character.

Upon the earliest appearance of these symptoms, no time must be lost. The one measure which has succeeded best in our hands has been vigorous artificial respiration continued for ten minutes to one-half hour. While this is being continued, an assistant should do cardiac massage and inject hypodermically camphor in ether, adrenalin and atropine. In a number of cases the prompt adoption of these measures, particularly artificial respiration, has been directly instrumental in saving life. As long as there is evidence of cardiac action, the attempts at revival of the patient should not be abandoned.

The injection may be followed by weak and irregular pulse, restlessness, headache, twitchings, and pain in the back and lower extremities. These symptoms usually subside.

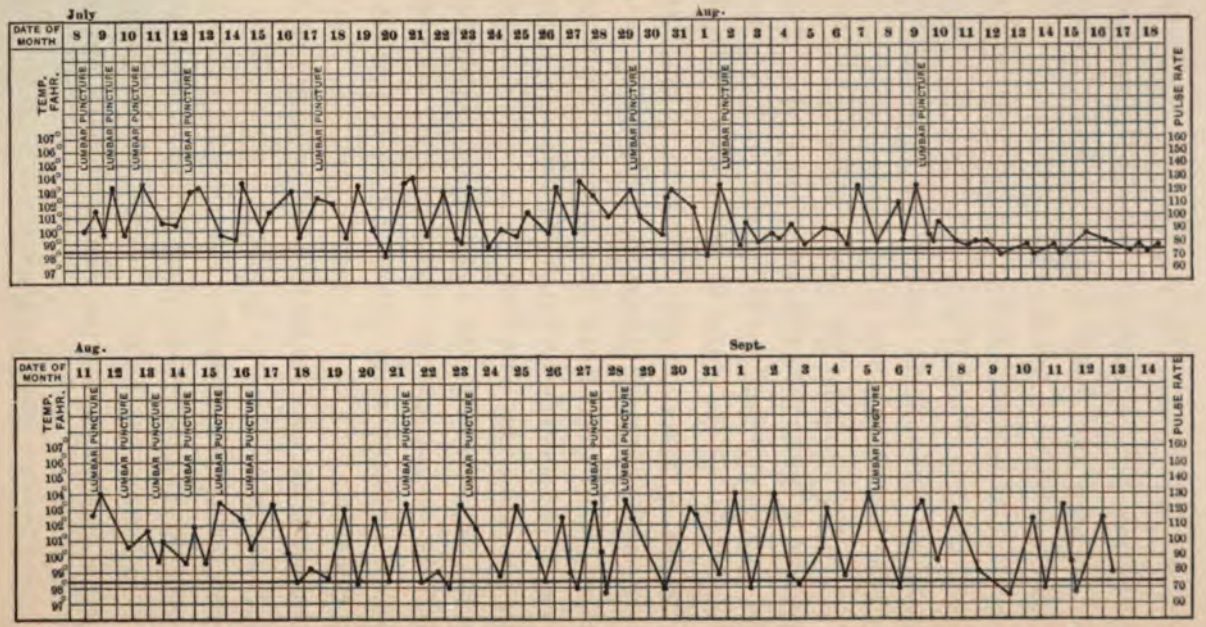
Levy has observed quite frequently a considerable rise in temperature and temporary aggravation of the meningitic symptoms, which he attributes to the rapid liberation of the endotoxin resulting from the bacteriolytic action of the serum. His opinion is based upon the fact that the temperature did not

rise when meningococci were no longer present in the fluid.

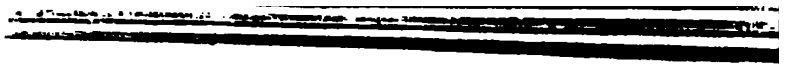
Causes of Failure with Serum Treatment.—Lack of success with the specific treatment may be due to several causes. When the vital centres in the brain are seriously compromised before the treatment is begun, little effect from the serum can be expected. In the fulminating cases the intense and rapid endotoxication can not well be combated by a serum whose detoxicating powers are comparatively feeble. In a certain number of cases complications having no direct connection with the disease, such as tuberculosis, bring about a fatal result, despite the beneficial action of the serum upon the meningococcus infection. In infants failure is often due to the early development of hydrocephalus. Last, but not least, of the factors which lead to failure is incomplete, insufficient, or unskilled use of the serum. The more favorable results obtained by those who are fully conversant with this method of treatment show the importance of this factor.

It must, however, be admitted that in a certain number of cases the infecting organism seems to be refractory to the action of the serum. This is probably due to the existence of strains of meningococci which are fast to the serum employed. It has not yet been definitely determined whether this is due to

CHART IV



Fever Charts of so-called Fast Cases of Meningococcus Meningitis.



resistance to solution by the intraleucocytic enzymes or to resistance to immune opsonins or bacteriotropins. It may be hoped that, by the employment of a number of these resistant strains for the production of specific antiserum, the cases refractory to the therapeutic action of the serum will become less and less numerous.

As an illustration of the so-called fast cases of meningococcus meningitis, the following two cases which recently came under observation showed how refractory these fast cases are to the antimeningitis serum at present supplied for treatment. The salient features of these cases were, that they both came from the same neighborhood, becoming infected about the same period of time, and that numerous injections of antimeningitis serum were given with no apparent effect. We would suggest, in view of the above facts, that strains of these meningococci should be properly cultured and inoculated for the purpose of establishing a fast serum for this class of cases. The accompanying temperature charts, on which the time of injections is indicated, will show how ineffectual the antimeningitis serum which has not been prepared from fast strains is in these cases.

As has been previously stated, Dopter finds that in some cases of meningitis the infecting organism is not the meningococcus but the closely allied para-

meningococcus. For these cases he advises the use of the antiparameningococcus serum prepared by him. Favorable results are reported by a number of French observers.

SYMPTOMATIC TREATMENT, ETC.

With the introduction of specific serotherapy, the symptomatic treatment of the disease has assumed secondary importance. There are a number of symptoms which at times must be temporarily combated with drugs or other measures until the serum shall have exerted its curative action. The most important of these are restlessness, headache, vomiting, insomnia, and convulsions. The restlessness is quite frequently greatly relieved by the use of bromides (gr. iii to x, according to age). Occasionally it is advisable to combine chloral hydrate (gr. ii to viii) with the bromides. This combination is also useful in diminishing the tendency to convulsions. The headache is best treated by an ice helmet applied intermittently to the head. The insomnia, which is a pronounced symptom in many cases, is often relieved by veronal (gr. ii to x) or trional (gr. ii to x), either alone or in combination.

It is customary to administer sodium or potassium iodide (gr. iii to x) empirically. It is claimed that it limits the inflammatory process and in the later stages

aids the absorption of the exudate. It is very doubtful whether such action is ever exerted by this drug.

Recently the use of urotropin has been advocated in this disease, as it has been shown by Crone that, subsequent to its administration by mouth, formaldehyde appears in the cerebrospinal fluid. We are not in possession of sufficient clinical data for the estimation at the present time of the value of this mode of treatment. At any rate, it is advisable to administer it in moderate doses (gr. ii to vii), combined with large quantities of water, to the patient as well as to all members of the patient's family, as a possible prophylactic measure.

Lumbar Puncture.—On theoretical grounds, we might expect that the withdrawal of fluid from the spinal canal would exert a definitely favorable effect on the disease. The removal of a certain amount of exudate and a more or less large number of organisms should diminish the inflammatory process in the meninges. Clinical observation and statistical data, however, have shown that lumbar puncture rarely exerts any but temporary effect on the course of the disease. It may temporarily relieve headache, restlessness, hyperæsthesia, and convulsive phenomena. But within twelve to twenty-four hours there is usually a return of symptoms present before

puncture. In extremely rare cases convalescence has set in after one lumbar puncture.

In the recent Silesian epidemic, Goeppert has shown that the mortality rate was not lowered by the use of lumbar puncture.

In acute hydrocephalus occurring at the onset of the disease, lumbar puncture is, without doubt, at times a life-saving procedure. In this condition is found the chief indication for the employment of this measure in the therapy of this disease.

In subacute and chronic cases it is indicated on the appearance of symptoms of increased intracranial pressure, such as Macewen sign, rise of temperature, headache, vomiting, convulsions, and increase of hyperæsthesia and rigidity. If no meningococci are present in the fluid, the serum should not be injected. Needless to add, spinal puncture is useless if there is occlusion of the outlets of the fourth ventricle.

Passive Hyperæmia (*Bier*).—This procedure has been recommended by Vorschuetz. He advises the application of the bandage for twenty-two hours after a preliminary lumbar puncture. He claims marked relief from this mode of treatment. Its field of usefulness remains to be determined.

Hot Baths.—This method of treatment was intro-

duced by Aufrecht in 1894, and has since been extensively employed. In many cases the use of the hot baths is followed by relief of pain, hyperæsthesia, delirium, and insomnia, and occasionally by a drop in temperature. Other patients experience no relief, and are indeed made worse by the manipulations. In cases where favorable action is exerted by the baths, they may be repeated three times a day. The temperature of the bath should be about 104° F. and its duration from ten to twenty minutes. At best the use of the hot baths is merely a palliative measure. They do not influence the course or duration of the disease.

Treatment of Complications.—The arthropathy is usually of such a mild nature that immobilization is ordinarily sufficient. For pain it is well to try moderate doses of aspirin and the local use of methyl salicylate. In suppurative arthritis, as we have seen, the serum has been successfully injected in the joint. The treatment of other complications, such as pneumonia, pleurisy, endocarditis, and paralysis, is carried out along the usual lines.

Treatment of Serum Disease.—It is well to administer a laxative in the form of castor oil or calomel. Alleviation of pruritus is usually accomplished by warm bicarbonate of soda baths and the local use

of 1 per cent. menthol lotion. In severe cases antipyrine may be administered.

Use of Vaccines.—As in the chronic cases the use of serum is not as efficacious as in the acute, it might be well to try the use of vaccines. Favorable results are to be expected only from the autogenous vaccines. These may be given in doses of 100 to 500 millions at intervals of four to five days.

Surgical Procedures.—A number of surgical operations have been proposed for the relief of intracranial pressure. In some of these the attempt has been made to secure permanent drainage. The most important of these procedures have been laminectomy, incision of the occipital ligament, craniotomy with through and through drainage. Haynes has devised an operation for draining the cisterna magna, for which he claims a minimum of risk, simplicity of technic, and ease of execution. Although his three cases, which were in a hopeless condition before operation, died, they were distinctly relieved for a short time by the procedure. We may say of all the surgical procedures thus far proposed, that, while temporary relief has occasionally followed, it remains to be proved that they are capable of exerting a durable effect on the disease.

GENERAL MANAGEMENT

Next in importance to the treatment with serum is that of the general care of the patient. The patient is kept in bed for at least a week after the temperature has become normal and the active symptoms have subsided. The proper nutrition of the invalid must be maintained. Generally the appetite is fairly well preserved and no great difficulty is encountered in persuading patients to take sufficient quantities of food. Occasionally, however, when the patient is comatose, nourishment by mouth is refused, and the problem of adequate nutrition becomes paramount. While rectal alimentation with peptonized milk, broth, and eggs is useful for a short period, it is rarely tolerated for any length of time. In this eventuality it becomes necessary to feed the patient by means of gavage or nasal feeding. At times this form of alimentation has to be maintained for a period of weeks. In breast-fed babies it is desirable to continue the breast feeding. Goeppert has shown that the prognosis is noticeably better in the breast-fed than in the bottle-fed babies.

During the height of the disease the diet should consist of milk, broths, and gruels. Soft diet should be resumed on the subsidence of febrile temperature. It is not desirable to restrict the diet unnecessarily, as the digestive functions are frequently not grea[illegible]

disturbed in this disease. In the chronic stage, forced feeding is demanded to overcome the emaciation which is so marked a feature of the disease.

To carry out the serum treatment under the best conditions, it is desirable that the patient be removed to a hospital. The chief indication for the repetition of the injections, as we have seen, is to be found in the examination of the cerebrospinal fluid. This can not conveniently be carried out while the patient is home.

Careful nursing constitutes an important part of the treatment. For very restless patients the bed should be well padded and the extremities wrapped up to prevent bruising. The danger of the development of bed-sores is to be guarded against by cleanliness, local use of alcohol and powder. In cases with marked retraction of the head, a pad should be placed beneath the occiput. In comatose and apathetic patients we must watch carefully for urinary retention. Evacuation of the bladder by catheter not infrequently is necessary. Retention may be present despite the existence of incontinence.

PROPHYLAXIS

The great difficulties to be overcome in the carrying out of efficient prophylactic measures against the disease are best realized when we recall some of the

facts that have been established regarding the manner of its transmission. We have learned that the dissemination of the disease occurs chiefly through the agency of healthy germ carriers. During an epidemic these are not confined to the immediate associates of each patient, but are generally diffused throughout the community. At such periods the number of healthy carriers has been estimated by Flügge to be from ten to twenty times that of the patients.

To check the spread of an epidemic in a locality would, therefore, require the detection and isolation of all germ carriers in a community, a task manifestly impossible of accomplishment. But even if this were done at the very earliest beginning of an outbreak, the time necessarily consumed in the process of isolation of the meningococcus from the nasopharynx would permit of the diffusion of the organism beyond the confines of the original focus of infection.

Complete isolation of all those who come in close contact with the patients on the assumption of their being possible germ carriers can not well be carried out for economic reasons. The infliction of such a hardship might perhaps be justified were we in possession of means of rapidly destroying the meningococcus in the nasopharynx. But it can not be

asserted that any of the local measures hitherto employed have proved measurably efficacious.

Pyocyanase, which was introduced by Escherich and used with apparent success by Jehle, exhibits a solvent action on the meningococcus in vitro. But this action is greatly reduced when it is added to albuminous solutions. Moreover, Haber has shown that pyocyanase loses its solvent action of the meningococcus when marked irritation of the pharynx and nose is present. Recently Wassermann and Kolle have advised the insufflation of dried antimeningitis serum. In eight cases, Kutscher succeeded by this method in rapidly ridding the nasopharynx of meningococci. Vincent advises inhalations of the following mixture:

Iodine	20.00
Guaiacol	2.00
Thymic acid	0.25
Alcohol (60 per cent.)	200.00

A small quantity of this mixture is put in a porcelain dish which is then placed in a bowl of boiling water to aid the evaporation of the mixture. The vapors are inhaled through the nose four or five times a day for about three minutes. The inhalations are supplemented by local applications twice a day of iodo-glycerin (1:30) to the tonsil and pharynx.

Gargling or rinsing of the mouth at frequent intervals with diluted peroxide of hydrogen is recommended. In France this method has attained considerable vogue and has been adopted in the army regulations. When we consider the protection afforded the meningococcus by the numerous folds of the mucous membrane of the nasopharynx, it does not seem likely that any local application, whether in the form of inhalation spray or insufflation, will prove effective in rapidly destroying all the meningococci in this region. At best we can only expect a reduction in the number of germs.

In view of these facts, we must content ourselves with the adoption of those practical measures which promise merely a reduction in the number of cases. All cases should be reported to the local health authorities. In the interest of the patient and the community, it is advisable to remove every patient to a hospital. Efficient serum treatment demands frequent laboratory examination of the cerebrospinal fluid, and this, except in rare cases, can not well be done while the patient remains home. The well-known rarity of germ carriers in hospitals renders the spread of the disease from these institutions very unlikely.

If the patient remains at home, he should be isolated, and the intercourse between the members

of the family and the outside world restricted as much as possible. The secretions of the nose and throat, the urine, and the stools should be disinfected as in typhoid fever. The throat should be sprayed several times a day with ½ per cent. peroxide of hydrogen. The bed and body linen should be disinfected, as well as all articles which are likely to be soiled with nasopharyngeal secretions. For disinfection, 2½ per cent. carbolic acid, ½ per cent. bichloride of mercury, or chloride of lime may be used.

The children in the family should not be permitted to visit the public schools for at least three weeks. Rarely is it advisable to close the schools. In severe epidemics large public gatherings should not be permitted by the health authorities. Young children should not be permitted to come in intimate contact with persons coming from infected localities.

Prophylactic Vaccination.—Sophian and Block, by injecting meningococcus vaccines in eleven students, demonstrated the appearance in the blood of agglutinins and antibodies. Hall, of Kansas City, gave three full vaccinations (500, 1000, and 1000 million killed bacteria) to 280 individuals of 50 families in which the disease occurred. None of these subsequently developed the disease. In Dallas, Texas, about 100 persons were vaccinated. Two

nurses, each of whom had two injections, developed the disease some weeks after the vaccinations. Both of them recovered. On account of the possible danger of developing the disease during the negative phase, it is advisable to make cultures of the nose and throat before the vaccination is done. If the meningococcus is found, it would be well to defer the injections until the organism has disappeared. On the other hand, in a number of instances the vaccination was followed by the disappearance of the organisms within a week. On account of the naturally slight degree of susceptibility to the disease, it will require many thousands of vaccinations to establish the prophylactic value of this mode of treatment.

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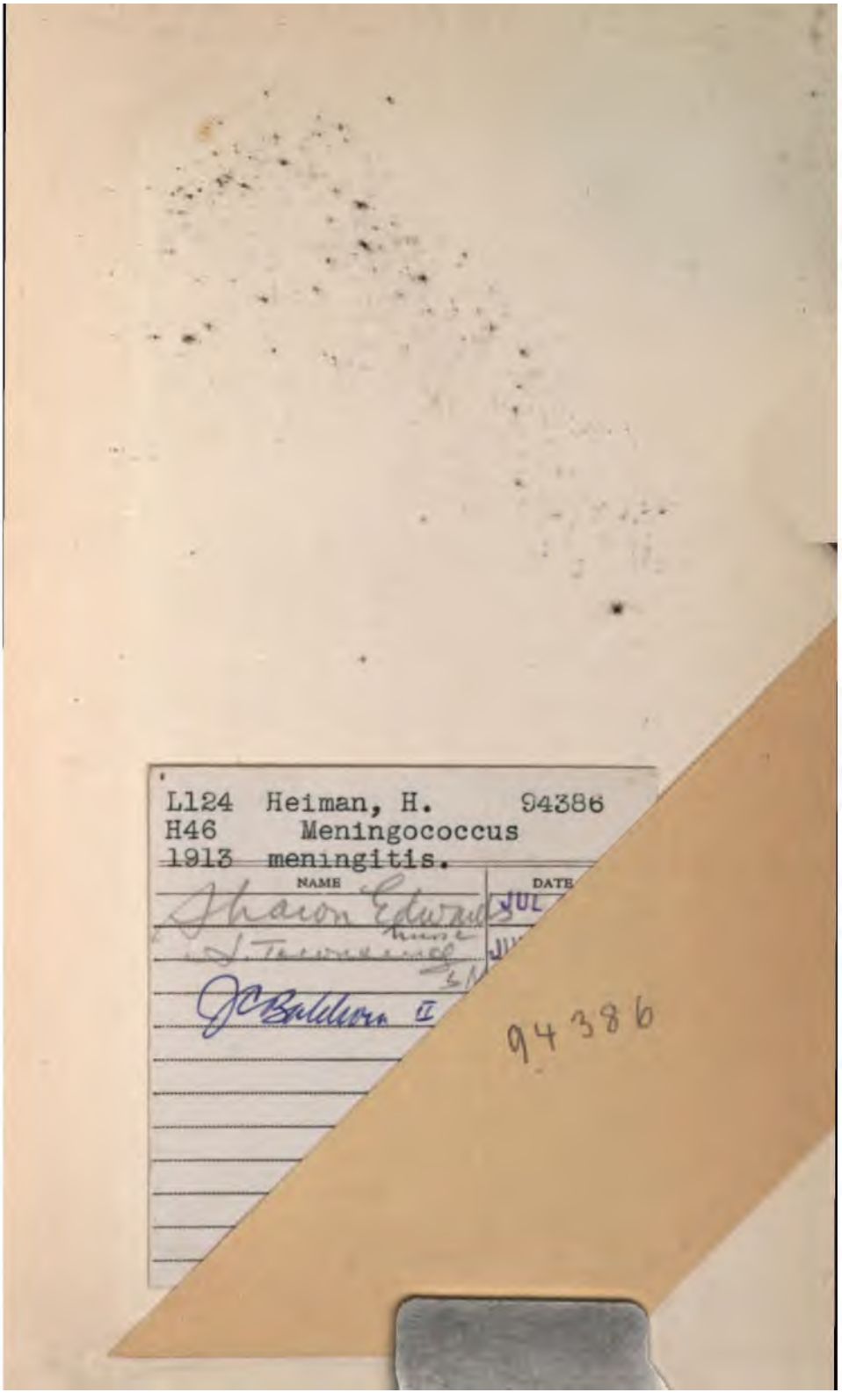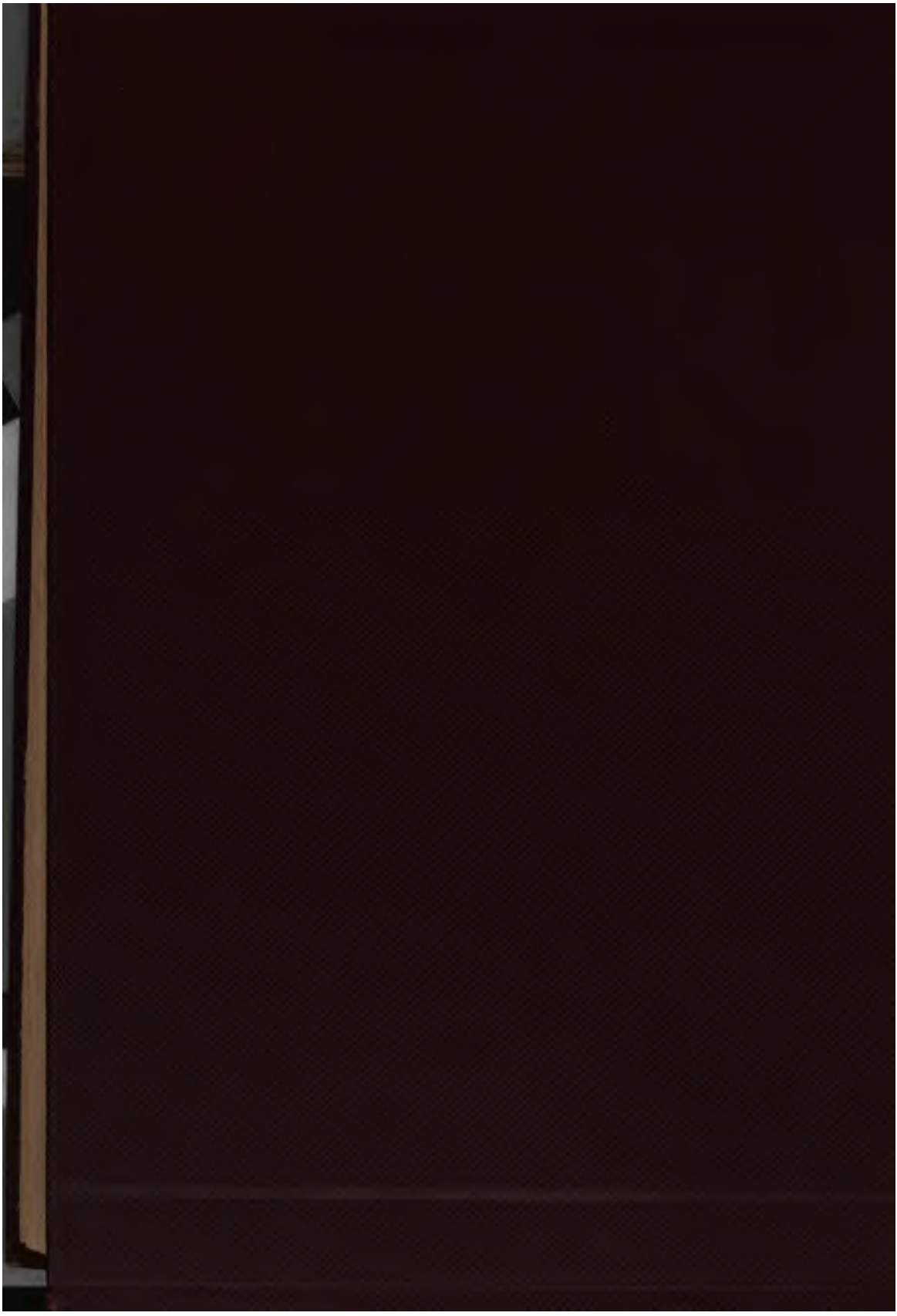
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